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A Molecular modeling facility had been setup for modeling of muscarinic agonists, antagonists and for receptor mapping. This facility included an Evans and Sutherland P330 vector terminal coupled to a VAX 785 minicomputer. Software available for the work included commercial modeling software such as ChemX, Gaussian, molecular mechanics (MM2) and in house developed software such as ARCHEM, and parameters for MM2.

The facility was used for modeling of muscarinic agonists, such as muscarine and its congeners, pilocarpine, tropine and antagonists such as atropine, quinuclicline, deptropine and others, to determine their conformational and electrostatic properties. From the conformational and energetic investigations of the ligands, bioactive conformations were obtained, which were fitted into the Beers and Reich and Shulman models and used to determine a pharmacophoric pattern common to all the ligands. From the superpositions of the common pharmacophoric patterns a topography of the muscarinic receptor was developed. The derived model of binding and docking to the receptor map, allowed a rational design of new ligands. Keywords:

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FOREWORD

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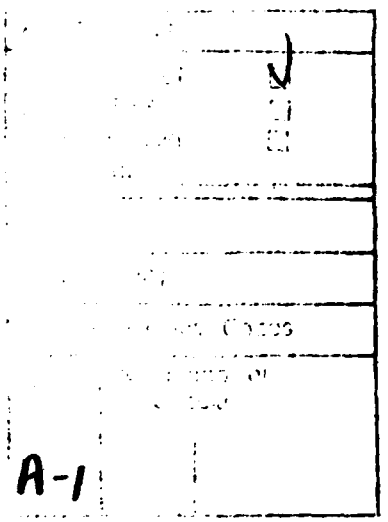

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MOLECULAR MODELING IN DRUG DESIGN FOR THE DEVELOPMENT OF ORGANOPHOSPHOROUS ANTIDOTES/PROPHYLACTICS

Final Report

Tamara Gund, Ph.D.

May 1, 1986

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I. STATEMENT OF PROBLEM UNDER STUDY

Our work has involved molecular modeling of muscarinic agonists and antagonists to determine their bioactive conformations. From the modeled ligands we hoped to derive a pharmacophoric pattern common to the ligands. This pharmacophoric pattern has enabled a topography of the muscarinic receptor to be derived which has facilitated the design of novel agonists and antagonists. The muscarinic acetylcholine receptor is responsible for many diseases incurred by man and for poisoning by nerve gas agents and other poisons. An understanding of the structure and function of the receptor and of the structural and electronic requirements for agonists and antagonists would enable a rational design of new antagonists which could serve as antidotes to these poisons.

II. BACKGROUND AND REVIEW OF LITERATURE

The malfunctioning of acetylcholine mediated transmission of nervous signals (which involves nicotinic and muscarinic receptors as well as acetylcholinesterase enzyme) is responsible for many diseases incurred by man[1], and interfering with cholinergic transmission is a key strategy in chemical warfare.[1c] Many nerve poisons function by inhibiting acetylcholinesterase, which prevents removal of released neurotransmitter, resulting in overstimulation of the cholinergic receptors. This produces biological responses that eventually may cause death.

An antidote may reverse the effects of acetylcholinesterase inhibitors by either binding to the receptor to reduce overstimulation by the agonist, or by reacting with the inhibitor, thereby reactivating the acetylcholinesterase enzyme so that it can resume its original function.[1c]

The acetylcholine receptor (AChR) is representative of a large class of membrane proteins responsible for the electrical activity of the nervous system. The receptor upon binding of an agonist responds by opening a channel and allowing ions to pass through the membrane. The ion flows produce electrical signals which cause nerve impulve activity, such as muscle contraction.

An agonist combines with the acetylcholine receptor to initiate changes in conformation states that results in the opening of the ion channel. The mechanism by which this process occurs is still unknown. The agonist is believed to remain bound to the receptor during activation, thus suggesting that the acetylcholine receptor can mold its conformation to fit the agonist structure.[2e] One method of studying the binding process is by structure-activity relationships. This endeavor is however difficult because most agonsits are flexible molecules and their bioactive conformations are undetermined. Rigid agonists facilitate the solution of this problem since the number of possible conformations is greatly diminished. The number of possible complementary conformational states of the receptor is likewise reduced.

Both the nicotinic and muscarinic receptors have been thoroughly studied,[2] although much more is known about the nicotinic system. The nicotinic receptor has been isolated from membranes, and reconstituted back into the membrane environment.[2f] The muscarinic receptor has not been isolated in pure form, because a convenient source which contains large amounts of the receptor has not yet been found.[3]

Since the actual structure of neither receptor is known, indirect methods have been used to gain insight into the structure, the binding mechanism, the geometry of the receptor site, and the bound conformations of agonists and antagonists.

Nonrigid molecules possess functional groups that are free to adopt a large number of spatial orientations. Predictions of the most probable conformers of these flexible molecules can be made either empirically, e.g. x-ray, NMR spectroscopy,[4] IR, etc., or theoretically, via calculations.[4] The assumption is often made that the preferred conformations are those that are most likely to be the active form of the molecule.[5] Molecules that have the same pharmacological effects are considered, and their conformational profiles compared for structural similarities.

The conformations of acetylcholine and other cholinegic ligands have been studied experimentally and computationally by many workers.[2,6,7] The types of calculations performed include Extended Huckel Theory (EHT), Intermediate Neglect of Differential Overlap (INDO), Perturbative Configuration Interaction of Localized Orbitals (PCILO), and ab initio calculations at the STO-3G level. Most of the calculations involved flexible molecules, and centered around deriving energy surfaces of fixed conformations with varying torsional angles of interest.[6]

Two receptor models for nicotinic and muscarinic binding were derived. One by Kier[7], shown in figure 1, is based upon comparisons of interatomic distances separating atomic centers of functional importance. The other, by Chothia and Pauling[8] (figure 2), is based on preferred values of relevant dihedral angles from x-ray crystallographic studies of potent cholinomimetics.[9]

Both models are based on fixed conformations of agonists and antagonists bound to the receptors, and both proposals fail to explain the activity of the reverse ester of acetylcholine. Donelsmith et al[4] found it necessary to invoke a model based on flexible receptors and ligands.

Schulman, Sabio and Disch[10] derived a preferred muscarinic pharmacophore (figure 3) by calculation of conformational energies and energies of interaction to a hypothetical carboxylate group (CO_2) for a coloumbic interaction and to an OH for a similar hydrogen bonding interaction. Their pharmacophoric pattern incorporates the distances between the receptor carboxylate (P) and hydroxy (Q) and the angle between them. This pharmacophore corresponds to an angle PNOQ between 60

and 117°. This pharmacophore does not however explain the binding of all the muscarinic agonists.

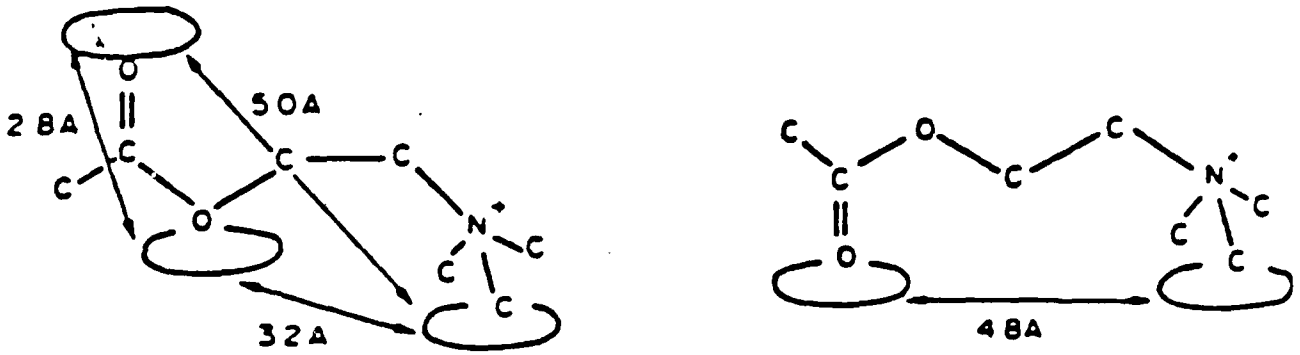


Fig. 1 The cholinergic receptor models of Kier showing the interaction of the preferred conformers of acetylcholine with (a) the muscarinic receptor and (b) the nicotinic receptor

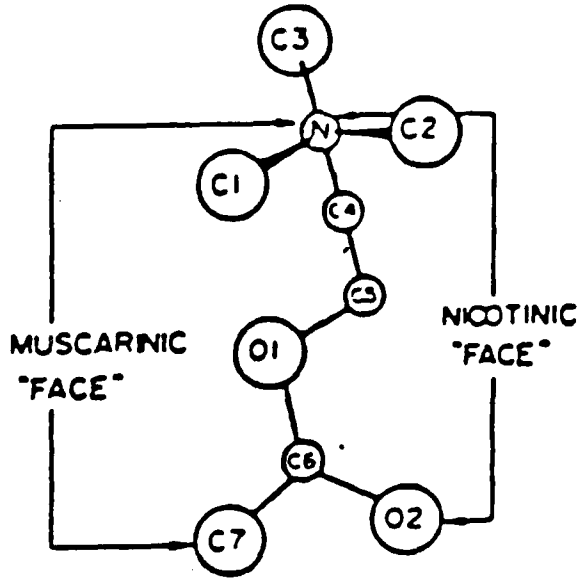


Fig 2. The Chothia-Pauling cholinergic model indicating the "nicotinic face" which consists of the quaternary nitrogen and carbonyl oxygen and the "muscarinic face" which is the quaternary nitrogen and acetyl methyl group.

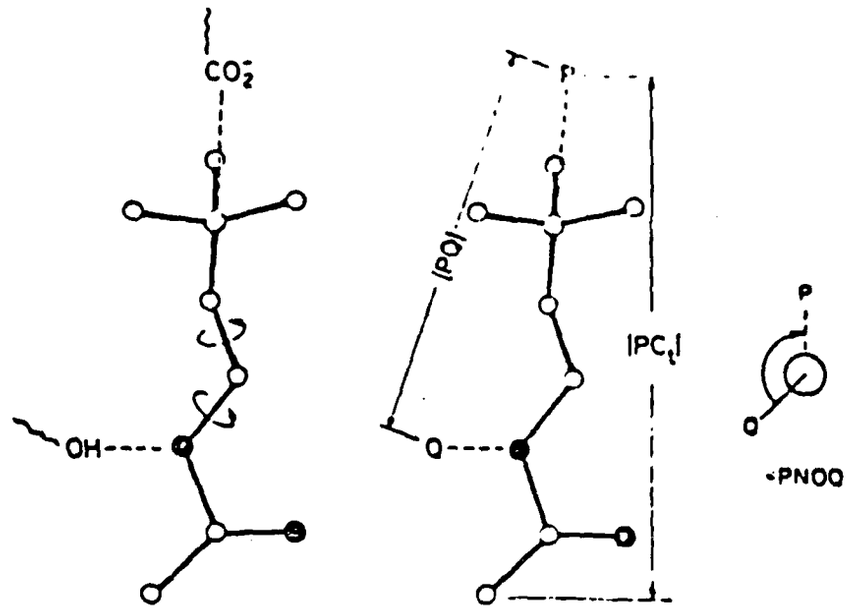


Figure 3 (a) Acetylcholine interacting with the receptor's carboxylate oxygen and an electrophilic group, such as a hydrogen-bonding proton. (b) The oxygen is indicated symbolically by *P* while the electrophilic site is located at the point of minimum electrostatic potential near the ester oxygen, denoted by *Q*. The interaction dihedral angle *PNOQ* is indicated on the right-hand side of the figure. Also shown are the distances $|PQ|$ and $|PC_t|$.

Beers and Reich[11] proposed a pharmacophoric distance for active muscarinic and nicotinic agonists. They predicted that the optimal distance between the site of coulombic interaction (quaternary nitrogen) and hydrogen bonding interaction (ester oxygen) for a muscarinic agonist is 4.44A.

Pullman , Courriere and Coubeils[12] performed quantum mechanical studies (PCILO) on acetylcholine, nicotine and muscarine to determine their conformational and electronic properties. Their conformational studies agreed with experimental data and their electronic studies revealed that the nitrogen on acetylcholine is almost neutral and the positive charges are spread over the three methyl groups, thus forming a large positive area for coulombic interaction with the receptor. Pauling[8] performed calculations on a series of anticholinergic substances, and discovered a consistent low energy conformation in all but two compounds, and determined which functional groups were necessary for pharmacological activity. The calculated energy of the consistent conformation was generally less than the crystal conformations, and for the two remaining structures the consistent conformations were only 2 kcal higher than the crystal structures. Weinstein[13] performed quantum mechanical calculations on 3-acetoxyquinuclidine and found that the molecule could adopt the gauche acetylcholine binding conformation. The interaction pharmacophore of the active species was defined by the electrostatic potential fields which were generated, and revealed a reactivity pattern identical with acetylcholine.

The structures of many agonists and antagonists of acetylcholine receptors are known. Activity and specificity varies with conformation and configuration of the molecule. A systematic computer graphic study of semirigid receptor agonists and antagonists could assist in correlating the structures of these drugs to their actions. Computer calculations now enable accurate predictions of preferred conformations[14], charge densitites, electrostatic potential contours and pharmacophoric patterns[15,16]. Without computers it is difficult to superimpose three dimensional molecular models to see how well two or more structures conform to one another, or to search for common structural elements. Also with models one can only guess at preferred conformations and relative energies, at charge densitites and electrostatic potential contours.

III. OVERALL PLAN

The overall strategy for studying the muscarine receptor and designing of antagonists which could serve as antidotes for nerve gas poisons is outlined below:

A. Obtain State of the Art Systems for Modeling Muscarinic Ligands and for Receptor Mapping

1. Hardware

a. Graphics
b. Computer

2. Software

a. Graphics - Input, Display
b. Calculations

B. Assemble a Project Team

C. Collect Suitable Muscarinic Ligands and Reliable Biological Data From the Literature

D. Establish a Viable Collaboration to Obtain New Compounds and Biological Data

E. Investigate Various Modeling Techniques for Applicability to the Research Problem

F. Apply Appropriate Techniques to Modeling Molecules of Interest

G. Draw Conclusions Related to Design of Muscarinic Antagonists

H. Derive a Geometric Model for the Muscarinic Receptor Site

I. Design Novel Muscarinic Antagonists for Synthesis and Pharmacological Testing

During the two years of this contract we have made substantial progress on all of the objectives as detailed in the remainder of this report. Since this was originally started as a three year contract and ended abruptly, all of the objectives were not completed and polished as originally anticipated. However the results of our research will be described and interpreted as well as possible.

IV. ACCOMPLISHMENTS

A. HARDWARE

The hardware that has been acquired for this project includes an Evans and Sutherland PS 330 Color Vector Terminal and two Advanced Electronics Design (AED) 767 color raster terminals, all interfaced to a VAX 11/780 super minicompouter.

B. SOFTWARE

At the start of this project the TRIBBLE[17] software from Dupont was available. At that time we were going to build a modeling system based on TRIBBLE, and use it for studying muscarinic agonists, antagonists and for receptor mapping. But since then, there has been an explosion of modeling software on

the commercial market, and so we dispensed with the idea of developing a complete software system and proceeded to acquire available modeling software through grants and purchasing. The following systems have been obtained and used for this project: (1) TRIBBLE from D. Pensak, Dupont de Nemours; (2) CHEMX, from Keith Davies, Chemical Design Ltd, Oxford, England; (3) CHEMLAB, from Molecular Design Ltd., San Leandro, California; and (4) SYBYL, from TRIPOS, St. Louis, Missouri. TRIBBLE was obtained at no charge; CHEMX and CHEMLAB were acquired through other grants, but updates have been obtained through this contract. SYBYL was awarded as a grant from TRIPOS; the first year's maintenance fee was paid by the university.

Our objective for obtaining these various modeling packages was to explore different modeling techniques in order to use optimal methods for modeling muscarinic ligands and mapping their receptor. In our experience, no single software package is adequate for solving this problem. Various portions of each package are superior to the others, and addition of programs, parameters and interfaces is still necessary.

Besides the above modeling packages, other calculational programs have been obtained and interfaced. These include Quantum Mechanical Methods: MOPAC (MNDO, MINDO) from M.J.S. Dewar (available through QCPE), Gaussian 82 from J. Pople (available from QCPE), PRDDO obtained from T. Halgren (Merck, Sharpe & Dohme); and a Classical mechanical method:, MM2, from Allinger (available from QCPE).

C. PERSONNEL

Much time during this period was taken up in assembling a first rate project team. Team members included a systems programmer, Dr. Rong Fa Liang, who was responsible for all software and hardware developments and maintenance; Dr. Liang was associated with the project from July 1, 1984 to March 31, 1986. The second team member associated with this project was a postdoctoral fellow, Dr. Mark Hermsmeier, who was associated with this project from August 1, 1985 until April 30, 1986. Dr. Hermsmeiers responsibilities included all applications research and some programming. A consultant, Kai Wen Jen, has been used for some specialized software development.

D. RESULTS

1. Interfacing of Programs

CHEMX, TRIBBLE, CHEMLAB, SYBYL and MOPAC have been interfaced so that data can be generated in one program and used in another.

We typically used TRIBBLE modules for structure generation and calculation. Data were then read into CHEMX or SYBYL for display and other manipulations. The following modifications in

TRIBBLE CHEMX, and SYBYL have been performed.

a. TRIBBLE mimized (MM2) structures (TRIBBLE CONFILE) can be viewed and modified in CHEMX ("modify/cursor") and sent back to TRIBBLE for MM2 minimization. The process can be repeated as often as one likes. The reason for this modification is that CHEMX minimizations are not as rigorous as the calculations in TRIBBLE, but the graphics input, display and modification features in CHEMX are superior to those in TRIBBLE. Also we used a revised version of mm2 which handles charges and TRIBBLE was the best program into which to insert our revised molecular mechanics program, since the commercial programs do not provide us with source code.

b. CHEMX sketched structures can be converted to TRIBBLE recognized files (TRIBBLE CON). These can then be sent for MM2 calculations and the optimized structures viewed by CHEMX. One problem encountered in interfacing different molecular modeling systems is that whenever an operation is performed, such as sketching of a structure using the graphics programs, a file of data is created which must be in the correct format for recognition by the next program. Different modeling systems use different file formats.

c. TRIBBLE, MOPAC and CHEMX have been interfaced so that graphics of CHEMX, molecular mechanics (MM2) and Semi-empirical calculations (CNDO) of TRIBBLE, and MNDO and MINDO of MOPAC can be utilized and data sent back and forth automatically. The procedure involves generating a CON file in TRIBBLE, converting this to a TRE file which can then be submitted to a CNDO calculation in TRIBBLE or sent to MOPAC for a better MNDO or MINDO calculation. The MOPAC charge files or CNDO charge files can then be read into the CHEMX electrostatics program for generation of an electrostatic surface. Programming was done to convert TRIBBLE TRE files to MOPAC input formats.

d. TRIBBLE, CHEMX and SYBYL have been interfaced so that structures that are stored and drawn using TRIBBLE or CHEMX can be viewed on the PS330 graphics terminal using SYBYL. The mechanics of the operation is to read TRIBBLE.con file to generate a .mac file in CHEMX. The .mac file is then modified for SYBYL input and a .mol file is generated. A program has been written for inserting MOPAC MNDO calculated charges into a .mol file.

e. TRIBBLE, CHEMLAB, and CHEMX have been interfaced so that files can be manipulated using any of the three programs and CHEMLAB files can be displayed using CHEMX or TRIBBLE graphics. The mechanism of the operation is to read a tribble.con file and generate a chemlab.chm file in chemx. Chemlab then reads the the correct chemlab atom type into the chm file, whose original atom type was zero.

2. Development of new programs

a. ESP - a program called ESP has been written which

calculates the electrostatic potential in three dimensional space. Calculated charges from MNDO or other programs are fed via the written interface program CESPREAD. The calculated potential can then be displayed on a PS300 using the written program ESDDOTSP. A display of color coded dots is then obtained where each dot represents a particular electrostatic potential which which can be accessed by using the data tablet. A program for displaying these dots, called AEDDOTSP, has also been written. The advantages of this program over other available programs is that electrostatic potentials can be clearly identified and turned on and off using the PS300 knobs. This program is also under our control to change and implement for different types of charge calculations and molecules. The other electrostatic programs in our possession did not come with source code.

b. AEDSYBYL - A graphics driver has been written for the AED 767 to display Sybyl graphics. The advantages of this has been that an AED is a raster display and therefore raster type graphics can be viewed which enable solid and space filling perspectives to be incorporated from the SYBYL program. Also in our environment we have two AED terminals and one PS300 terminal, so with this additional possibility more workers will have access to the Sybyl software.

c. ARCHEM - A software package has been developed for calculation of electrostatic potentials and fields in a given volume of space, such as at the van der Waals surface or at other desired points in space. The program is useful for generating all types of molecular surfaces of molecules. The calculations are performed on the VAX 11/785 or the CYBER 205 supercomputer and results are plotted in color on an HP 7550A 8 pen plotter. Electrostatic potentials are calculated from partial charges derived from MNDO (MOPAC) or Gaussian ab initio calculations. The program is also useful for plotting two and three dimensional drawings of molecules.This is a very useful addition since much of our time is spent in preparing reports and presenting our work.

3. Parameterization of Allingers MM2 program.

The normal version of MM2 does not handle charges properly and was not parameterized for ammonium salts. Since all the molecules that we are presently considering are ammonium salts, MM2 was modified for us to handle charges by Dr. T. Halgren of Merck Sharpe and Dohme, Rahway, N.J. Parameters were developed in conjunction with Dr. J. Snyder, of Searle Pharmaceutical Co., Chicago, Ill.. Parameters were developed from x-ray data on cyclic and non-cyclic ammonium salts and futher refined by calculations at the 6-31G* level. We had to alter the normal MM2 program within TRIBBLE to incorporate these changes.

4. Molecular Modeling Approach

Biological activity is a result of ligand-receptor binding. It is well known that drug - receptor interactions are analogous to a lock and key concept where complementarity is needed to involve a biological response. However, drug - receptor interactions are governed by electrostatic attractions, as well as geometric factors. We have therefore calculated conformational and electronic properties of the agonists and antagonists chosen for modelling and from the active and inactive agonists determined a receptor topography which together with the other properties of the ligands is useful for design of new ligands. Our approach involved (a) generating three dimensional structures from two dimensional sketches, (b) calculating minimum energy conformations by the revised MM2 program; (c) identifying other conformations by systematic rotation of rotatable bonds; (d) identifying the pharmacophoric pattern; (e) comparing structures according to steric energies and physical parameters, bond lengths, bond angles, and non-bonding distances; (f) calculating partial atomic charges using MNDO (MOPAC); (g) calculating electrostatic potential energy contour surfaces; (h) generating a receptor topography by the excluded volume technique of Marshall; (i) fitting of new agonists and antagonists into the derived receptor map.

5. Agonists and Antagonists Modeled

The agonists that were modeled for this contract are shown in Chart I, and include muscarine **(1)**, epiallomuscarine, **(2)** epimuscarine**(3)**, allomuscarine **(4)**, cis/trans 2,3 dehydromuscarine **(5,6)**, cis/trans muscarone **(7,8)**, cis/trans F2268 **(9,10)**, 5-methylfurmethide **(11,)**, TFTM **(12)**, arecoline **(13)**, F2581 **(14)**, four isomeric 3-trimethylamino-2-acetoxy-trans-decalins **(15-18)**, pilocarpine **(19)** and tropine **(20)**. The antagonists that were modeled include atropine **(21)**, deptoprine **(22)** and quinuclidine **(23)** and are shown in Chart II.

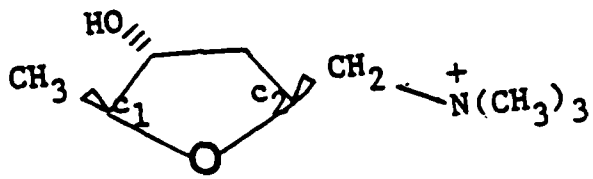
6. Optimization Studies for Agonists (1-13) Involving rotation of one rotatable bond at a time.

Optimization studies were carried out by first deriving possible conformations using the revised version of MM2 and in some cases MNDO. Other conformations were searched by systematic rotation of rotatable bonds. Steric energies were calculated for all conformations and nonbonding distances for the bonding sites N.....O were calculated according to the procedure described below.

Beers and Reich[11] and others[5] have proposed that for the muscarinic receptor ligands, the major sites of interaction between the ligand and the receptor involves a coulombic and a hydrogen bonding interaction involving the quaternary nitrogen and the ring oxygen, respectively. Beers and Reich[11] proposed that the distance between the coulombic and the hydrogen bonding interaction (at the van der Waals extension of the ring oxygen) should be 4.44A^{o}. We therefore calculated the distances between the quaternary nitrogen and ring oxygen extension for the minimum

energy structures which were generated. Table I lists the steric energies, extended N...O distances, and dihedral angles of the side chains for the lowest energy structures. As can be seen, the Beers and Reich distance of 4.44A^{O} is not achieved in the lowest energy conformers which have extended N1110 distances that are either too low or too high. We therefore searched for other low energy conformations. Where a rotatable side chain is present we used the MM2 dihedral driver option to generate conformations with 30^{O} incremental rotations over a 360^{O} range. Tables II-XVII indicate the correlation of dihedral angle with steric energy and extended N...O distance. In all cases several conformations with the critical distance around 4.4A^{O} are possible. The conformations most likely to be important for bioactivity are those within 5 kcal of the global minimum[10]. These are indicated in the Tables. The smaller the energy difference between the global minimum and the possible bioactive conformation the more likely that the conformation can be achieved.

The procedure that we used to calculate the nonbonding distances between O....N at the Van der Waals extension of oxygen is illustrated for muscarine and is as follows:



Muscarine

a. Assume C_1 - C_2 - 0 to form a triangular plane on the x,y axis, z=0 (figure 4)

b. Set up three dummy atoms according to the bond length of C^1C_2, C^1O,C^2O

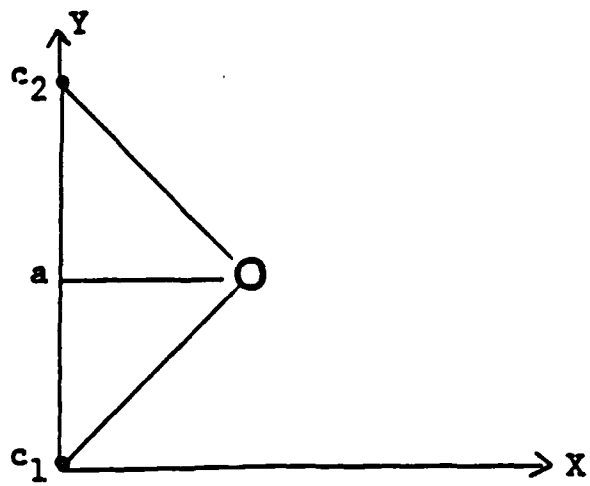


FIGURE 4

c. Form two right triangles and calculate the length 0-a using the phythagorean theorem. Bond lengths C_20,C_10, and C_1C_2 can be obtained from the MM2 output and $aC_1 = 1/2\ C_1C_2$.

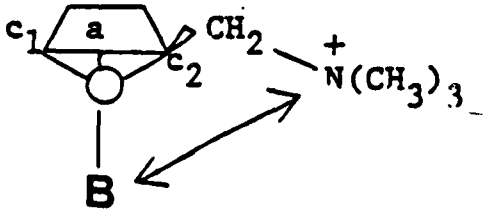
By the phythagorean theorem:

$$(OC_2)^2 = (0a)^2 + (aC_2)^2$$

$$(0a)^2 = (0C_2)^2 - (aC_2)^2$$

$$0a = \left[(0C_2)^2 - (aC_2)^2\right]^{1/2}$$

Adding 1.74A + 0a = new distance (a-0-B) in a straight line extension. We then calculate the non-bonding distance from N to B.



a. Muscarine and its Isomers (1-4)

Chart III gives structures for the lowest energy conformers of agonists **1-13** shown in Chart I.

Tables II-V show the results of dihedral driver calculations for muscarine, epiallomuscarine, epimuscarine and allomuscarine. The lowest energy (global minimum) structures were given in Chart III. The calculated energies were similar (Table I, about 28 kcal). The ring conformations and the side chain dihedral angles were also similar about 70°). Extended N...0 distances (about 3.0A°) were not within the Beers and Reich distance of 4.44A°. Incremental rotation of the side chain and MM2 optimization produced conformers with better N...0 distances but higher energies. Those with steric energies within 5 kcal of the lowest are considered most accessible conformers. For muscarine, epiallo-and epimuscarine these are conformations with dihedral angles of 150° and 180°, and for allomuscarine conformations with dihedral angles of 120, 150 and 180°. All of these have extended N...0 distances between 4.1 to 4.8A°.

b. Cis/trans-2,3-dehydromuscarine (5,6), cis/trans-Muscarone (7,8), and cis/trans-F2268 (9,10).

Tables VI-XI show the results of dihedral driver optimizations for the titled compounds. As for the muscarine isomers, the global minimum structures have extended N...0 distances which are similar and too short (3.1 to 3.5A°), and similar dihedral angles (about ±70°). Potential bioactive

conformations for all of the above except trans-F2268 have dihedral angles of 120, 150 and 180° and extended distances between 4.1 to 5.0A°. Trans-F2268 has the best extended N...O distances (4.3 to 4.94A°) at dihedral angles of 180° and 210°. Trans-muscarone can achieve the potential bioactive conformations with difficulty since the difference in steric energy between the lowest energy conformer and these varies by 6 to 16 kcal. The extended N...O distances for the trans isomer are also a bit high. (4.9 to 5.0A°).

c. 5-Methylfurmethide (11), TFTM (12), Arecoline Derivatives (13) and F-2581 (14).

The 5-membered ring agonists, 5-methylfumethide and TFTM (Tables XII and XIII) are analogous to the muscarine analogs with global minimum structures having dihedral angles of about 70° and extended N...O distances between 3.0 - 4.0A°. Better N...O distances are obtained for conformers with dihedral angles between 120 and 240° (N...O 4.3 to 4.6A°). For TFTM however, to attain the projected bioconformations a distortion of 6 to 9 kcal of energy must occur.

F2581 (Table XIV) has fewer conformational possibilities. The six membered ring exists as a chair, and for the 1,4 trans isomer the two substituents are preferentially in diequatorial positions. However, the diequatorial isomer (energy 33.08 kcal) does not fit the bioactive scheme (extended N...O distance of 5.1A°). When we attempted to model the diaxial conformer we did not get a final energy and the extended N...O distance was too short, 3.67A°.

The arecoline derivatives (Tables XV-XVII) that we modeled included the NH_2, monomethyl and dimethyl ammonium salts. The best ring conformation for all of these analogs was a half-chair. The global mimimum for all of the congeners (NH_2, NH, CH_3 and N-CH_3, CH_3) was the s-trans conformer (180° dihedral angle indicated by asteriscs). Although this conformation had the lowest energy, in each case the extended N...O distances were too high (5.6 - 5.8A°).

It has been proposed that the muscarinic receptor binds to the quaternary ammonium group and to the ester ether oxygen while the nicotinic receptor binds to the ester carbonyl oxygen.[11] The conformers with dihedral angles between 0-60° had the best extended N...O distances, 4.4 to 4.7A°, but their energies were high (7 to 8 kcal higher). We don't know at this point whether binding to the receptor can lower these energy differences. Perhaps binding could occur initially by hydrogen bonding to the oxygen of the s-trans conformation, followed by rotation around the single bond to achieve the coulombic interaction at the quaternary nitrogen.

d. 3-Trimethylamino-2-acetoxy-trans-decalins (15-18)

Optimized structures and energies have been calculated for

the four possible isomeric 3-trimethylamino-2-acetoxy-trans-decalins shown in Chart I. Only the diequatorial and axial/equatorial ($-N(CH_3)_3$/-OCOCHuld be optimized using MM2 calculations. However using MNDO calculations all four isomers were minimized and their N....O distances calculated.

Calculations derived from molecular mechanics shown in Table XVIII in principle agree with those from MNDO (Table XIX). The highest energy conformer, the diaxial ($N(CH_3)$-$OCOCH_3$) appears to have a distance of N....O of about 4.1 A^o which is close to the Beers and Reich distance. The diaxial isomer is only 6.6 kcal higher in energy than the more stable diequatorial isomer. The difference in energy between the diequatorial and axial/equatorial isomers is 5 kcal, however all three of those isomers have short N....O distances (about 3.1-3.6 A^o). Optimized structures derived from MNDO for the four decalin isomers are shown in Chart IV.

e. Pilocarpine (19).

As an agonist, pilocarpine is rather large (Chart I and V). In order to properly evaluate this molecule three difficulties must be overcome. (1) The nitrogen atoms in the protonated imidazole ring are not parameterized in the molecular mechanics program mm2. (2) There are two rotatable bonds providing two degrees of reedom in the conformational energy surface (Chart VI).

Using mm2 calculations four optimized structures were derived. Table XX summarizes dihedral angle versus steric energy versus Beers and Reich distance for the four conformers and Chart VII gives the three dimensional representation of the four pilocarpines 1-4.

It is difficult and time consuming to develop new force field parameters. The conformation of the planar imidazole ring is quite rigid. Therefore during all the minimizations the five heavy atoms of the ring are fixed to one conformation, so that the force field parameters are constant. The conformation chosen is that of the x-ray crystal structure of pilocarpine hexachlorogermanate (Chart VIII). The remaining atoms were allowed to move to minimum energy positions under the constraint of the dihedral angle driver.

f. Atropine (21), Dibenamine (22) and Quinuclidine (23)

Minimized structures of Atropine, Dibenamine, and Quinuclidine are shown in Charts IX, X and XI. All were minimized using mm2 calculations. Tables XXI, XXII, and XXIII give results of the dihedral driver calculations. For all three antagonists calculations were performed first by allowing ring conformations to change while a 360^o rotation was performed about angle tau_1. Then the ring conformation was kept constant with a nonbonding N..O distance of 4.483 A^o. This allowed calculation of relative steric energy differences between the various conformations.

For Atropine, conformations with angles of 60, 90, 120, 180, and 240 fit the Beers and Reich distance. For Deptoprine Beers and Reich distances are best met with dihedral angle conformations of 90, 120, 150,and 180 degrees. The best conformation with lowest angle is that with dihedral angle of 110.8 degrees. The other conformations have very high energies. For quinuclidine, there are several conformations which fit the Beers and Reich distance and are also within a reasonable steric energy margin. The best conformations are those with dihedral angles of 0, 30, 150, 180,and 210.

7. Optimization Method Varying Two Rotatable Bonds

A method to systematically search conformational space by independent rotation of two bonds and subsequent energy calculation was implemented. This procedure generates a projection of a 3-dimensional surface, where the x and y axes are the torsion angles rotated. Equal energy levels are shown as contours on this map. The local minima are easily identified. However, this is a rigid rotation procedure and each point is not minimized. Therefore the structures corresponding to the local minima are minimized using MM2. In our experience there is very little change in conformation with this minimization.

If there are more than two freely rotatable bonds it is possible that this method will not adequately search the important space and minimum energy conformations will not be evident. However, by careful examination of the rotatable bonds and by judicious selection of the initial geometry it is possible to obtain all the local minima. The method will be illustrated with a conformatonal search for pilocarpine (19),tropine (20) and atropine (21).

a. Pilocarpine (19)

When this method of conformational search was applied to Pilocarpine it yielded the same minimum conformations as was obtained previously and reported above. (The conformational energy diagram is shown in figure 5).

b. Tropine-Atropine (20,21)

There are two possible conformations of the bicyclic system (chair and boat conformations of the 6-membered ring). The boat conformation is not stable and reverts to the chair conformation when the energy is minimized using MM2. NMR experiments reveal that the solution conformation of tropine is the chair.

The two torsion angle conformational search of tropine is shown in figure 6. From the graph two local minima are found. Upon minimization both are found to have nearly identical energies. In fact the two conformations are mirror images, which

is also evident from the symmetry of the conformational energy map.Table XXIV lists the two tropines (A and B) and their structural and energetic features as well as fitting into their various models. Chart XII shows the actual computer drawn structures of Tropine A.

The local minimum associated with the predicted bioactive conformation (to be discussed later) can be estimated from its antagonist analogue, atropine. Both of these compounds have the same primary binding site structure. Atropine, however has much more steric bulk at the tail end of the molecule. The conformational energy surface is more complicated because there are 3 important rotatable bonds. Three conformational energy maps were made with the third torsional angle in three different positions. The maps are quite similar and show that there are no hidden local minima. The local minima from each of the maps is minimized using mm2 to obtain the results shown in Table XXV.

Like Tropine, Atropine has two local minima in its conformational energy map (Figure 7). The added structure of Atropine causes the minima to have energies that differ by 2kcal/mole. If the bioactive conformation of Atropine has tau1=170^{o} and tau2=100^{o} and if Atropine and Tropine bind to the receptor in the same way, then the bioactive conformation of Tropine should have tau1=170^{o} and tau2=100^{o} as well. This corresponds to the A conformation of Tropine (tau1=-163^{o} and tau2=96^{o}). Tropine B conformation also fits the various criteria with tau1=-67^{o} and tau2=-89^{o} (Table XXIV). One of the derived bioactive conformers of Atropine (Atropine A) is shown in Chart XIII.

8. Derivation of Bioactive Conformations

a. Agonists (1-20)

Bioactive conformations of agonists have been derived by considering the models of Beers and Reich and Schulman, Sabio, and Dish described above. We are fitting our modeled agonists into these two models, trying to derive an optimal bioactive conformation for each. In this report we describe our correlations with the Schulman and Reich models for fourteen of the agonists modeled, muscarine, epiallomuscarine, epimuscarine, allomuscarine, cis/trans dehydromuscarine, cis/trans muscarone, TFTM, cis/trans F2268, 5-methylfurmrthide, and pilocarpine. There are twelve conformations for each molecule corresponding to the twelve thirty degree increments of dihedral angle NCCO.

We are attempting to correlate activity with closeness of fit of bioactive conformation The activity of the various stereoisomers differ by nearly three orders of magnitude and any reasonable model should reveal this difference. Four parameters are plotted as a function of the NCCO dihedral angle. The first parameter is the steric energy as calculated by mm2; the second parameter is the Beers and Reich distance calculated using ChemX; the third parameter is Schulmans dihedral angle PNOQ; the fourth parameter is Schulman's distance PQ. The limiting values for the

four parameters are a five kcal energy barrier above the global minimum, a distance of 4.44A° between the N...O, a PNOQ angle of about 117° and a PQ distsnce of 6.6 to 6.8A°.

The requirements of the steric energy restricts the energy to be not more than five kcal/mole above the global minimum. This limits the angle PNOQ to be approximately between 0 and 180° for each of the stereoisomers. This shows that the stereochemistry of the attached methyl and hydroxyl groups do not affect the conformational energy surface enough to explain the difference in bioactivity of the stereoisomers.

Figures 8-15 illustrate the plots of the four parameters for agonists **1-8**. Muscarine(**1**), epimuscarine (**2**), and epiallomuscarine (**3**) fit the four parameters best at dihedral angles of 150°. Allomuscarine (**4**) fits the four parameters best at a dihedral angle of 180°. The conformer with dihedral angle of 150° does not fit the Schulman PNOQ angle of 117°. Dehydro(**5**) and epiallodehydromuscarine (**6**) fit the four parameters at dihedral angles of 140 - 150°. Cis muscarone (**7**) also fits the parameters at a dihedral angle of 150°. However, trans muscarone (**8**) fits the parameters at dihedral angle of 90°.

Figures 16-20 illustate the plots of the four parameters for agonists **9 - 12** and **19**. Cis/trans F2268 both fit the four parameters best at dihedral angles of 150°. For TFTM the best bioactive conformation which fits all four parameters is the one with dihedral angle of 150°o. 5-Methylfurmethyde also fits the four parameters well at a dihedral angle of 150°.Pilocarpine has many possible conformations. Here we present six possibilities, however none of these fit the four parameter criteria very well. For pilocarpine 1, the Beers and Reich distances are a bit too high. The best fit here is between 120 to 180° dihedral angle. The energies fit well. The Schulman distance PQ fits only the 180° dihedral angle and the PNOQ angle fits a dihedral angle of 240°. Pilocarpine 2 fits the Beers and Reich distance best at 180° dihedral angle. The energy at this angle is a bit high, about 15 kcal above the global minimum. The Schulman PQ distance does not fit and the PNOQ angle also does not fit. Pilocarpine 3 does not fit very well either.Pilocarpine 4,5, and 6 similarly do not completely fit the criteria. We are checking further into the conformations of pilocarpine to see if we can derive one that fits the four parameter criteria. Pilocarpine is a weak agonist and being that it does not fit the bioactive criteria could account for its weak potency.

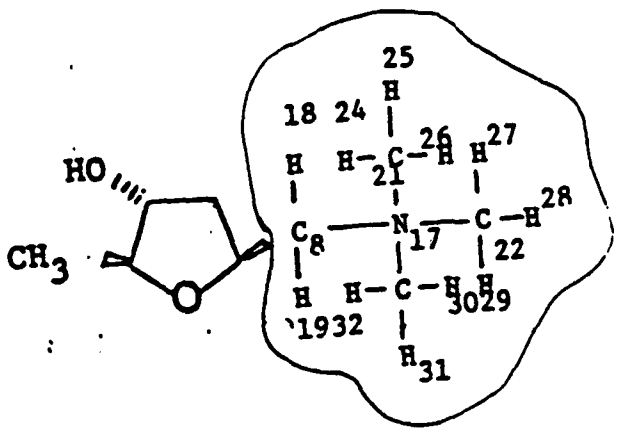
The four parameters for derivation of bioactive conformations for tropine were shown in Table XXIV and the possible bioactive conformation is given in Chart XII.

b. Antagonist (21)

The derived bioactive parameters for atropine are given in Table XXV and the computer drawn structures are given in Chart XIII.

9. Calculation of Partial Charges

Partial charges were calculated for the molecules in Chart I. For all cases MOPAC (MINDO) was used, and in some cases MINDO and CNDO charges were derived as well. We were testing various methods for partial charge generation. Tables XXVI - XXXI give the results of partial charges calculated by the different methods. Charges were calculated for the lowest energy conformation and for all the most probable bioconformations (those with extended N...O distances around 4.0 - 4.8A° and within 7 kcal from the global minimum). These results are given in Appendix A. Cationic head charges were calculated for the various conformers. An example of this calculation is illustrated for muscarine. The cationic head is illustrated below and is within the enclosed region.



Taking the sum of the charges in that region gives a charge of 0.917 for muscarine. A comparion of MNDO and CNDO data indicates a better correlation with literature data for MNDO derived charges. It is well known that for tetrasubstitued nitrogens, the positive charge resides on the peripheral methyls and hydrogens and not on the nitrogen.[12] MNDO calculations agree with this result, while CNDO calculations give a positive nitrogen. MINDO calculations are very similar to MNDO. As can be seen from Tables XXVI to XXXI, and Appendix A there is a small variation in cationic head charge with isomer, conformation and agonist. A larger head charge would result in a better agonist-receptor interaction. Muscarine and its Cis/trans isomers epiallomuscarine, epimuscarine and allomuscarine all have similar cationic head charges of about 0.9 esu., while their dehydro analogs, cis/trans 2,3 dehydromuscarine have slightly larger cationic charges, 1.0 esu. The cationic head charges for cis/trans muscarone are about 0.94 esu for all conformers.

The cationic head charge of 5-methylfurmethide (1.02 esu) coincides with that of 2,3 dehydromuscarine, while the cationic head charge of TFTM is closer to muscarine and its isomers (0.93 esu). Arecoline, H,H, H,CH_3, and CH_3,CH_3 is also close to

muscarine (0.92 esu). The cationic head charge of arecoline (s-trans)is 0.9363, and of s-cis is .9235. the cationic head of tropine is lower, 0.6568.

Charge calculations that have been carried out for pilocarpine and for the three antagonists, atropine, dibenamine and quinuclidine are given in Appendix A. Cationic head charges for these compounds are as follows: pilocarpine, 0.532, atropine. 0.65, dibenamine , 0.73, and quinuclidine 0.65. The cationic head charge for pilocarpine is unusually low and may correlate with a lower activity of pilocarpine compared to the other agonists.

10. Derivation of Electrostatic Potential Contours

Electrostatic Potential[18] contours were generated from the MNDO charges for the lowest energy and the possible bioactive conformations of the agonists in Chart I. Table XXXII summarizes the agonists, steric energies, dihedral angles, N...O distances, and electrostatic contour levels that were generated. Most of the electrostatic potentials were contoured at 20,30,100, and 150 kcals and some at 30,120 and 160 as well. Electrostatic potentials were generated as repulsive potentials to an incoming positive charge: the larger the potential the more positive the area, and increased binding to the receptor might be expected. Since there is a net charge of +1 on these agonists, there are no negative potentials but there are areas of more or less positive charge. We checked the conformations for the highest and lowest contouring values. The largest potential obtained for any of the agonists is 160 kcal. The lowest potential falls at 20 kcal. The most positive region is always around the methyl and methylene substituents on the nitrogen (cationic head). The lowest potentials are found near the oxygens. This substantiates the idea of coulomic interaction occuring at the amino group and hydrogen bonding interaction at the oxygens. From the plotted maps it is difficult to see significant differences. We plan to compute electrostatic potential difference maps to unveil subtle differences in the electrostatic field for different analogs.

The methodology is illustrated in figure 21 where illustrations for muscarine are given. Muscarine has a maximum electrostatic potential of 150 kcals: this region is shown in black and surrounds the N-methyls. The lowest potentials are found around the ring oxygens and these are shown in red.

11. Receptor Mapping

Receptor mapping involves three steps. First a collection of both weak and strong agonists are selected and the bioactive conformations of the strong agonists are chosen. Second each of the agonists are fitted to a common template. Third the union of the Van der Waal volumes of the strong agonists is subtracted from that of the weak agonists. The resulting volume represents that volume which is potentially occupied by the receptor and

is called the receptor map. It is assumed that a strong agonist will not occupy any of the space which the receptor occupies, while a weak agonist will occupy a portion of the space which is occupied by the receptor.

The strong agonists chosen for this work are muscarine,cis-muscarone, cis-F2268 and 5-methylfurmethide. The weak agonists are diastereomers of muscarine, ie. (-)muscarine, epimuscarine, epiallomuscarine and allomuscarine (Chart XV). These are flexible compounds. In order to choose the bioactive conformations the Beers and Reich pharmacophore model, the Schulman pharmacophore model and the conformational energies were considered. Each of these agonists have one important rotatable bond. The dihedral angle driver routine of the MM2 program was used to calculate the energy as the NCCO bond is rotated. For each of the conformations generated the pharmacaphore geometries are calculated using CONRAM. The results for muscarine are plotted in figure 22. The conformations which meet all the criteria have a NCCO dihedral angle equal to about 150 degrees. Therefore this dihedral angle was set to 150 degrees in each of the eight agonists.

The conformation of muscarine where the NCCO angle is equal to 150 degrees was chosen as the template on which all the other agonists were fitted. The FIT command in SYBYL was used to do this. The four atoms shown marked with an "x" in figure 23 were selected as the atoms to be fitted. They were given equal weight. These atoms were chosen because they will best preserve the Beers and Reich pharmacophore model in the receptor map.

The unions of the volumes of the four strong agonists and the four weak agonists were made using the MVOLUME command in SYBYL. The strong agonist volume was subtracted from the weak agonist volume to obtain the excluded volume. This is the receptor map, ie. the best estimate of the Van der Waal surface of the receptor binding site.

The bioactive conformations of several other agonists and antagonists were determined. These conformations were fitted to the muscarine template and placed in the receptor map. These compounds include pilocarpine, tropine and atropine.

Note 1: CONRAM is an in-house program which calculates bond lengths bond angles and dihedral angles within a molecule. It can place dummy atoms in strategic positions. For example, it can place an atom 1.74 angstroms from the oxygen atom along the bisector of the COC angle as is required to calculate the Beers and Reich distance.

Note 2: The FIT command in SYBYL is a least squares program which adjusts the orientation of a target molecule to minimize the sum of the distances between the atoms selected in the target molecule and the atoms selected in the template molecule.

Note 3: The union operation in the MVOLUME command in SYBYL selects all points in space which are inside the Van der Waal surface of any one of the chosen molecules.

The union of all the active agonists is shown in Chart XVI(a). The union of all the actives and inactives is shown in Chart XVI(b). Yellow represents all the actives. From the difference between the inactives and actives emerges the receptor map shown in purple with muscarine in the middle in green. This is shown in Chart XVI(c). Charts XVI(d and e) show the map with a dot structure of muscarine in the middle both in mono and stereo views. The dot structures of muscarine show the van der waal surface taken up by muscarine and better illustrates the cavity space that agonists occupy. We started using this map for fitting of other agonists that were not used in the original calculation. Chart XVI(f and g) show the fitting with pilocarpine and with tropine in the dot representation. The fit for both agonists is very good. We were interested in determining the fit of antagonists toward the agonist map. We fitted atropine in the line and dot structure (Chart XVI, h and i) and found that the binding regions namely the coulombic and hydrogen bonding regions fit very well in the map but the antagonists always had a bulky region that did not fit into the map. In this case it is a phenyl group which probably has its own binding region which is important for antagonists.

12. Design of New Ligands

The techniques of conformational analysis, which includes deriving preferred conformations and testing these by fitting into the Beers and Reich models, Schulman models and 5 kcal energy constraints from the lowest energy conformer, superposition and fitting into derived receptor maps are being used to design new ligands which could be synthesized and tested for agonist/antagonist potency. In this report we present two rigid analogs of tropine xtropine-a and xtropine-b (Chart XVII), and two rigid analogs of atropine, xatropine-1 and xatropine-2 (Chart XVIII). All four compounds were designed to capture the best bioactive conformations of tropine and atropine. All four compounds fit the Beers and Reich and Schulman models, and all are energetically feasible. Table XXXIII gives the derived parameters. Chart XVI (j and k) shows their fitting with the nonrigid analogs and into the receptor maps. In all cases the fit is good.

V. DISCUSSION

Many of the goals presented have been accomplished. The modeling system developed is a combination of written and commercial software. At the beginning of the contract there wasn't any software available to do this research with, therefore we expected to develop more of the software used. But since this field has exploded and is progressing at such a rapid rate, we dispensed with the idea of developing all the software and

proceeded to obtain software through grants and purchases. One computer scientist developing software could not compete with the commercial companies that have started developing software specifically for this field.

Computer Assisted modeling of ligands has given insights into some of the important factors that may be controlling potency of muscarinic ligands. Since binding is a result of fit between the receptor cavity and ligand conformation and complementarity of charge between receptor and ligand we proceed to develop a method where we consider both conformations, energy, and charge of the ligands. Since at this time we do not know the structure of the receptor we first began to consider the properties of the ligands and correlate these factors with potency.

The five membered ring cyclic analogs of muscarine show the same general conformational trends. The lowest energy (global minimum) for each 5 membered cyclic agonist falls at a dihedral angle of about 70^{o} ($\pm 5^{o}$). These minimum energy structures, however, all possess extended N...0 distances substantially smaller than the $4.44A^{o}$ required for muscarine activity according to the Beers and Reich hypothesis[11]. To achieve the requisite N...0 distance, rotation of the side chain is needed. The conformations with an appropriate extended N...0 distance ($4.4A^{o}$ $\pm .4$) usually fall at dihedral angles of $120\text{-}210^{o}$, with preference for most cases at $150\text{-}180^{o}$. However, with this rotation an increase in steric energy is observed. The energies vary from 2 to 16 kcal above the minimum. Bioactive conformations were derived using a combination of energy allowances for the various conformations generated (within 5 kcal of the lowest energy conformer) and fitting the conformations into the two published models of Beers and Reich[11] and Schulman, Sabio, and Disch.[10] For the five membered cyclic agonits the most probable bioactive conformers were those that had dihedral angles between $150\text{-}180^{o}$. The antagonists that were considered also had similar binding regions that could be superimposed on the agonists.

For some of the agonists these conformations are difficult to achieve due to a large energy barrier: this is true for <u>trans</u>-dehydromuscarine, and for <u>trans</u> muscarone.

At this point it is not clear how the conformational aspects govern activity. All of these molecules have other functional groups which could be involved in binding, perhaps to another site. Schulman, Sabio, and Disch[10] have performed calculations on some of the same molecules and have reached similar conclusions.

Partial charges were calculated and contoured around the molecules. This gave indications of where the positive and negative sights were and some indication of the relative strengths of the charges at the various positions. Partial charge calculations and electrostatic potential energies agree that where another carbonyl, hydroxyl or ether oxygen is present, this is a high electron density region and thus possibly subject

to an additional hydrogen bonding interaction, which potentiates the binding to the muscarinic receptor. Alternatively it could hinder binding if that binding is to other than the muscarinic receptor. The molecule might compete for which receptor to bind to. Stronger potency is associated with a larger cationic head charge.

The electrostatic work was not totally completed because the contract ended abruptly and the personnel had to leave the project. The effect of remote OH groups and other groups is still to be explored in greater detail.

Receptor mapping studies which were performed were effective in deriving a plausible receptor topography which is useful in giving insights into potency of ligands and has been used to design new ligands for synthesis and testing.

VI. CONCLUSIONS

So many factors are involved between the initial binding of a drug to its receptor and the final outcome of potency of the drug. Computer calculations can only give us insights into some of the factors that are involved but when combined with synthetic and pharmacological approaches it can be effective in deriving a model for binding requiremets and in designing new ligands with desired properties .

We have shown that conformational, electrostatic and receptor mapping studies give insights into the properties of the drugs described. These factors can be further used to design new ligands which should be synthesized and tested for potency. Many questions remain unanswered partly due to the complexity of the problem and partly because the project ended sooner than expected. We feel that muscarine has emerged as a template upon which other ligands can be modeled and compared both conformationally and electrostatically. For the future a better separation of conformation versus electrostatics versus solvation needs to be explored and an actual model that quantitates these contributions needs to be developed.
remains

VII. REFERENCES

1. a)Review: G.G. Lunt and R. Harrison, Biochem. Soc. Trans. 8, 693-694 (1980): b) Review: S.M. Aquilonius, "Parkinson's Disease, Curr. Progr. Probl. Manag. Proc. No. Eur. Symp. 1979," U.K. Rinne, M. Klinger, G. Stamm, Ed., Elsevier, Amsterdam, 1980, 17-27; c) M.C. Gerald, "Pharmacology, An Introduction to Drugs", and Ed. Prentice Hall Ince., Englewood Cliffs, N.J., 1981, p. 128-147, L.A. Kepner and O.L. Wolthuis, Eur. J. Pharmacol., 48, 377-382 (1978).

2. a)Review: J. Hucho, Trends in Biochem. Sci., 6, 242 (1981); b)M.J. Ross, M. Klymkowski, D.A. Agard and R.M. Stroud, J. Mol. Biol., 116, 299 (1977); c) C.F. Stevens, Nature 287, 13 (1980); d) M.W. Klymkowski and R.M. Stroud, J. Mol. Biol. 128, 319-334 (1979); e) C.E.Spivak and E.X. Albuquerque, Progress in Cholinergic Biology: Model Cholinergic Synapses, edit, by I. Hanin and A.M. Goldberg, Raven Press, New York, 323-357, (1982).

3. E. Heilbronn and T. Bartfai, "Progress in Neurobiology", Vol. 11, 1978, pp. 171-188 Pergamon Press.

4. K.W. Reed, W.J. Murray, E.B. Roche and L.N. Donelsmith, Gen. Pharmac., 12, 177-185 (1981).

5. L.B.Kier, "Molecular Orbital Theory in Drug Design", Academic Press, N.Y., 1971, p. 163.

6. B.R. Gelin and M. Karplus, J.Am. Chem. Soc., 97, 6996 (1975) and references 3-12 therein.

7. L.B. Kier, Molec. Pharmacol., 3, 487 (1967).

8. P. Pauling in "The Conformation of Anticholinergic Substances," J.C. Stoclet, Ed., Adv. Pharmacol., Ther., Proc. 7th Int. Congi. Pharmacol., Pergamon, 1979, p. 302, P. Pauling and N. Datta, Anticholinergic Substances: a single consistent conformation, Proc. Nat. Acad. Sci. U.S.A. 77, 708-712 (1980).
P. Pauling and T.F. Petcher, Chem. Comm. 1001-1002 (1969).

9. R.W. Baker, C.H. Chothia, P. Pauling and T.J. Petcher, Nature, 230, 439-445 (1971).

10. J.M. Schulman, M.L. Sabrio, and R.L. Disch, J. Med. Chem., 26, 817 (1983).

11. Beers and Reich, Nature, 228, 917 (1970).

12. B. Pullman, Ph. Courriere and J.P. Coubeils Mol. Pharmacol. 7, 397-405 (1971).

13. H. Weinstein, R. Osman, W.D. Edwards and J.P. Green, Int. J. Quantum Chem., Quantum Biol., Symp. 5, 449 (1978).

14. a) U. Burkert and N.L. Allinger, "Molecular Mecahnics" ACS Monograph 177, ACS p. 1-319 (1982); b) N.L. Allinger and Y.H. Yuh, Quantum Chemistry Program Exchange, Prog. No. 395 (1980).

15. C. Humblet and G.R. Marshall, Drug Devel. Res., 1, 409 (1981).

16. a) P. Gund, Progr. Mol. and Subcell. Biol., 5, 177 (1977; b) P. Gund, Ann. Repts. Med. Chem., 14, 299 (1979).

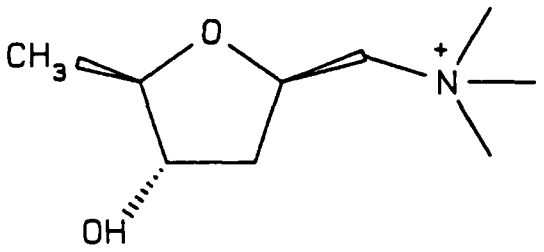
17. a) D.F. Eaton and D.F. Pensak, J. Am. Chem. Soc., 100, 7428-9 (1980); b) D.A. Pensak, Industrial Res. and Dev. 74 (1983).

18. P. Politzer, "Chemical Applications of Atomic and Molecular Electrostatic Potentials", (P. Politzer and D.G. Truhlar, eds.) Plenum Press, New York, 1981.

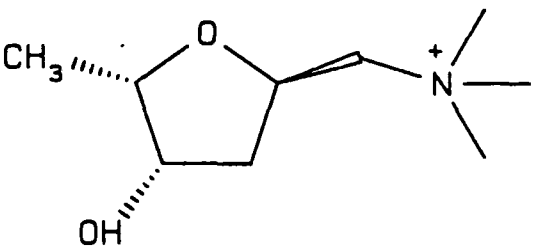
VIII. CHARTS, FIGURES AND TABLES

CHART I

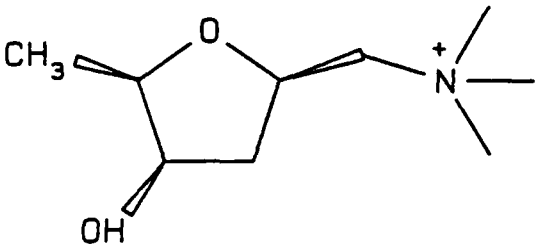
AGONISTS THAT WERE MODELLED USING TRIBBLE FOR STRUCTURE INPUT



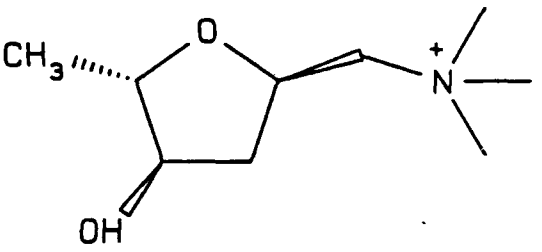
a. muscarine



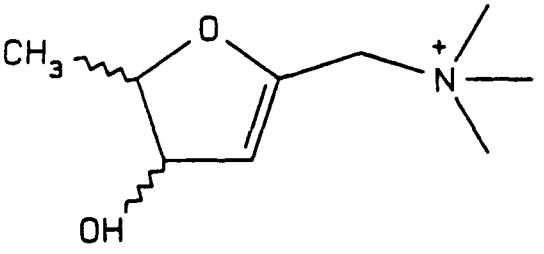
b. epiallomuscarine



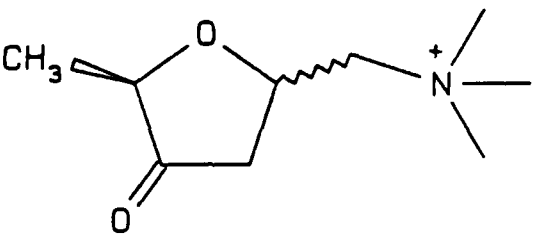
c. epimuscarine



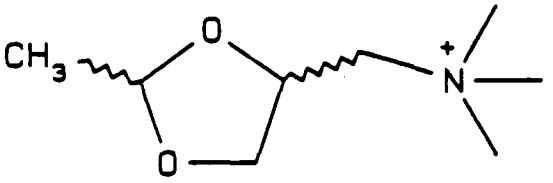
d. allomuscarine



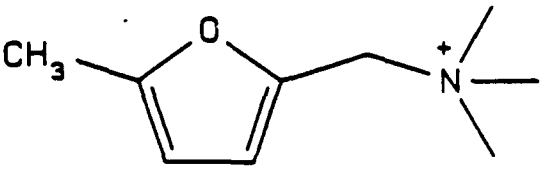
e. cis/trans 2, 3 dehydromuscarine



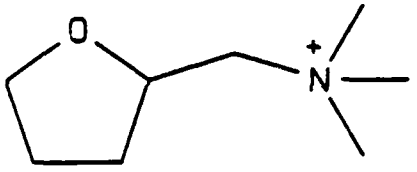
f. cis/trans Muscarone



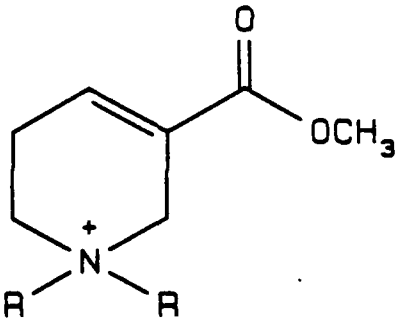
g. cis/trans F2268



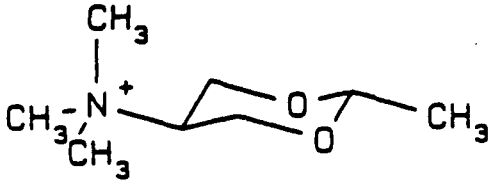
h. 5-methylfurmethide



i. TFTM



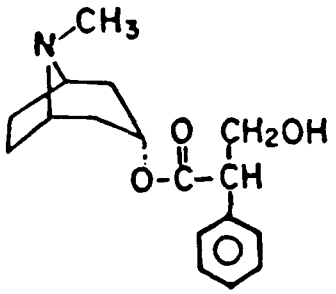
j. arecoline



k. F2581

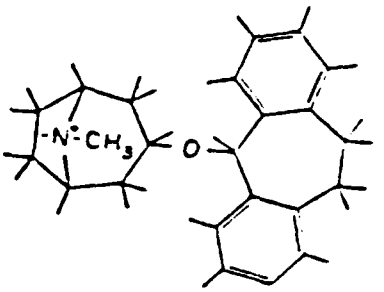
CHART II

ANTAGONISTS MODELED



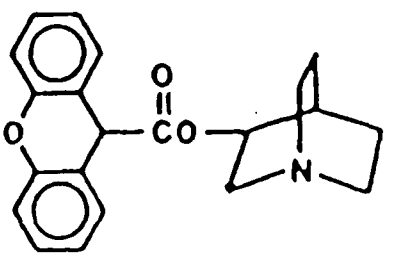
Atropine

21



Deptoprine

22



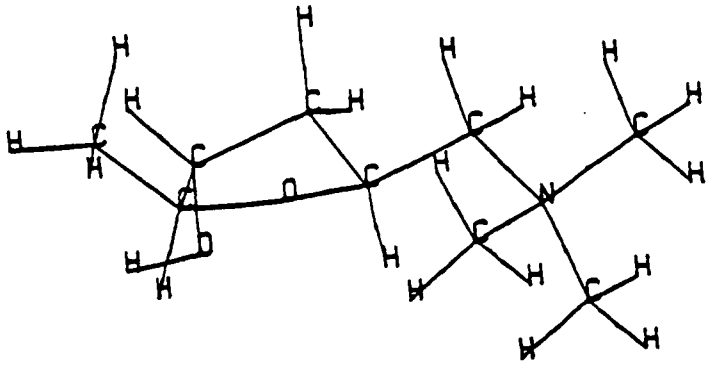
Ouniclidine

23

CHART III

GLOBAL MINIMUM STRUCTURES

a. Muscarine



b. Epiallomuscarine

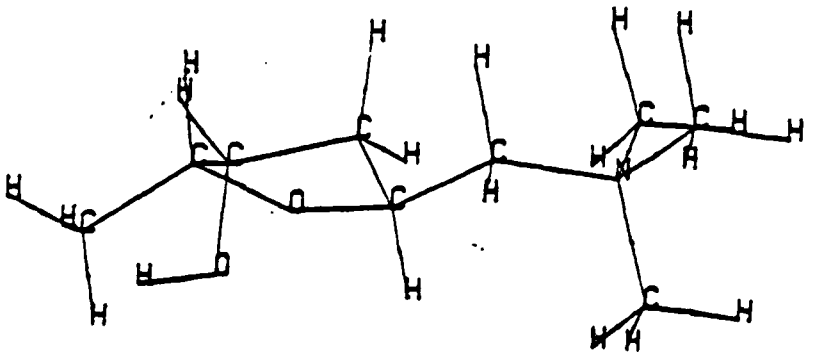
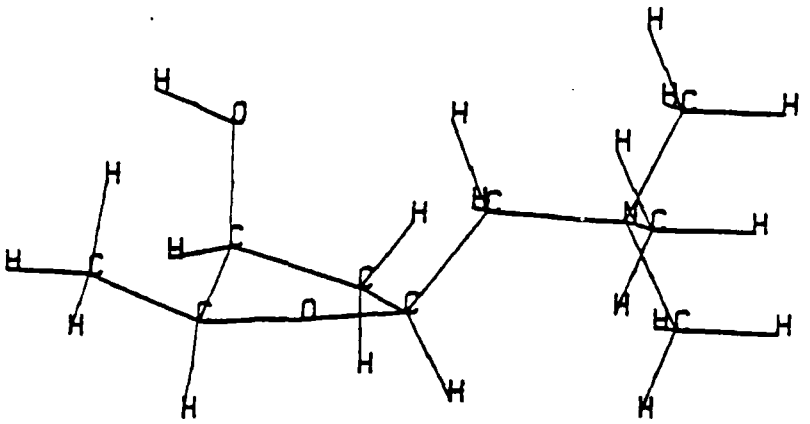


CHART III

GLOBAL MINIMUM STRUCTURES

c. Epimuscarine



d. Allomuscarine

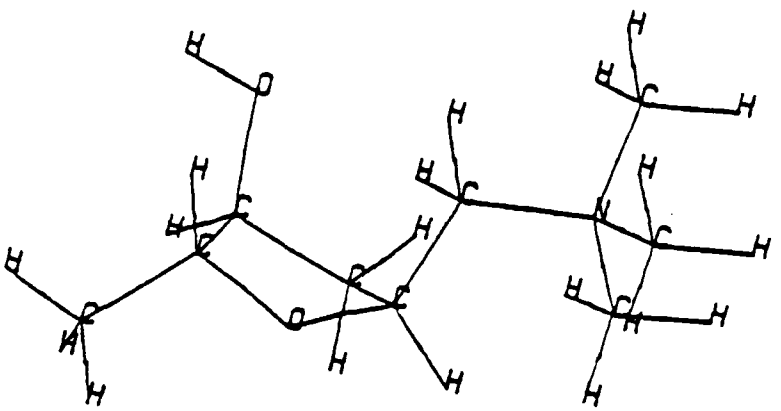
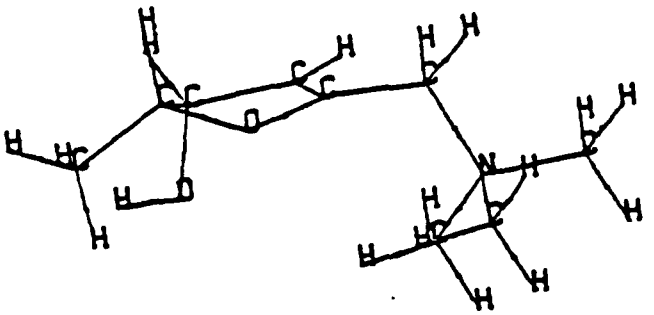


CHART III

GLOBAL MINIMUM STRUCTURES

e. Dehydromuscarine (2,3)(cis)



f. Dehydromuscarine (2,3)(trans)

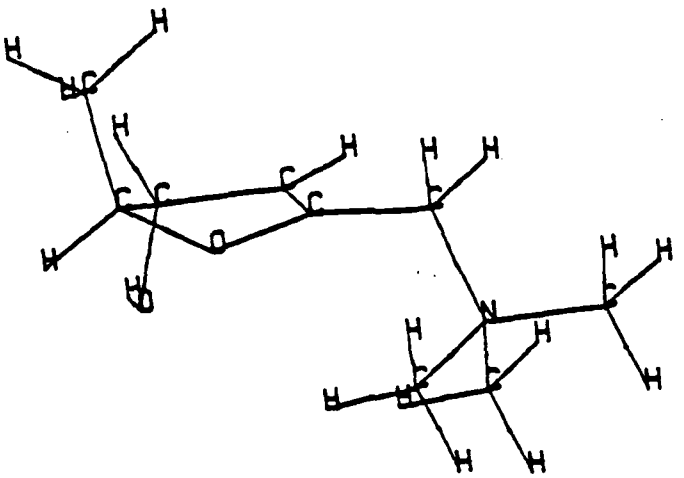
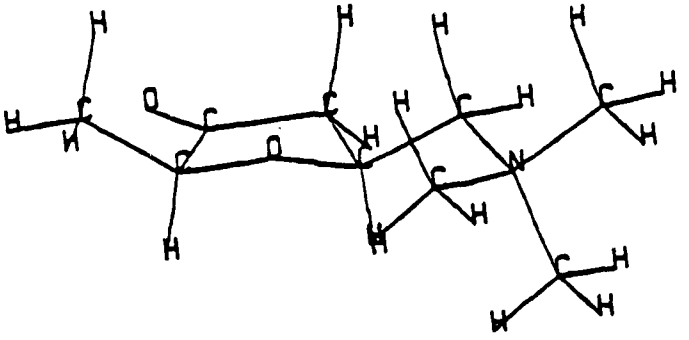


CHART III

GLOBAL MINIMUM STRUCTURES

g. Muscarone (cis)



h. Muscarone (trans)

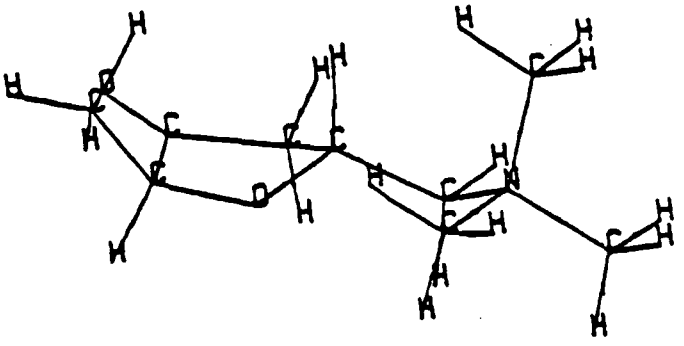
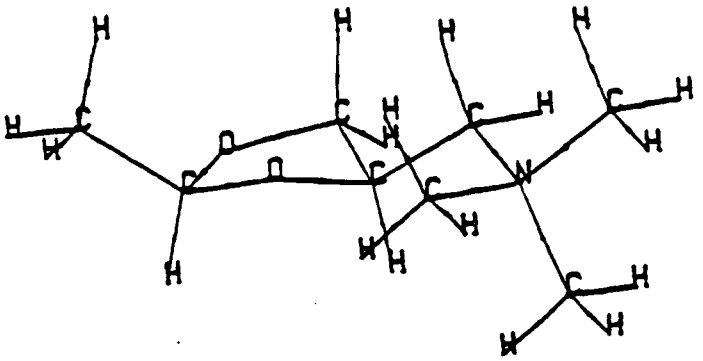


CHART III

GLOBAL MINIMUM STRUCTURES

i. F 2268 (cis)



j. F 2268 (trans)

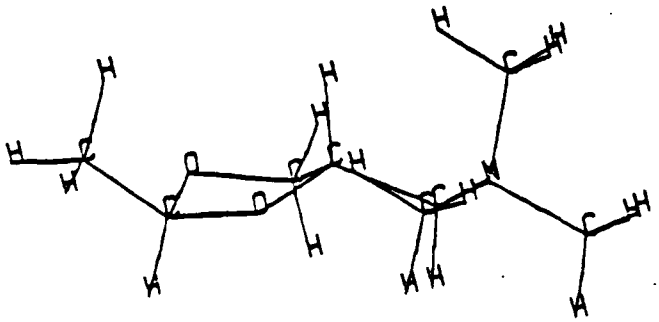
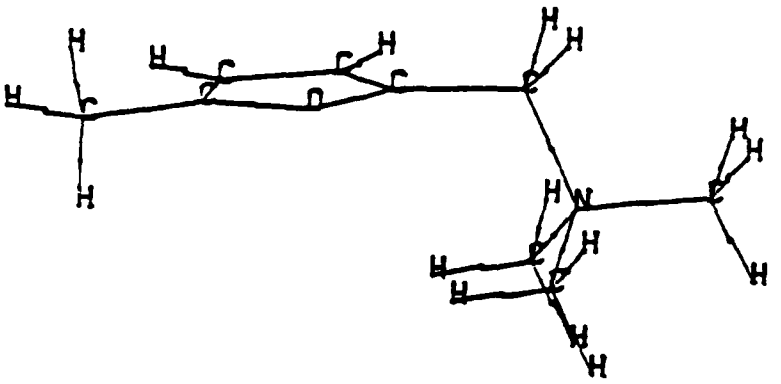


CHART III

GLOBAL MINIMUM STRUCTURES

k. 5-Methylfurmethide



l. TFTM

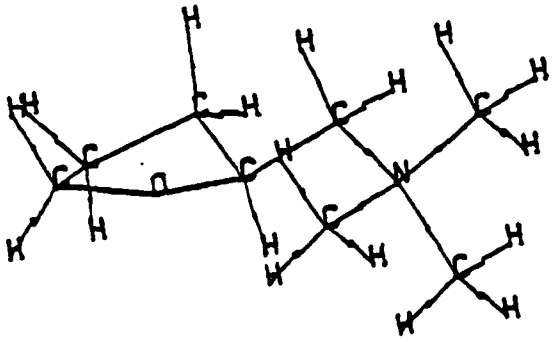
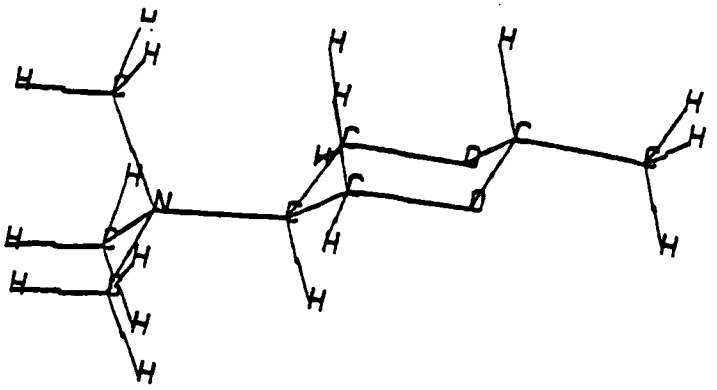


CHART III

GLOBAL MINIMUM STRUCTURES

m. F 2581



n. Arecoline (H,H)

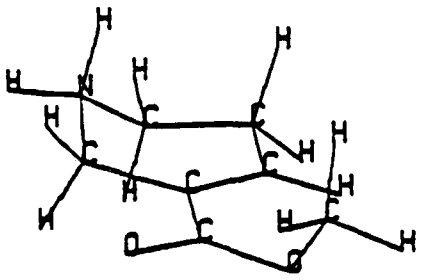
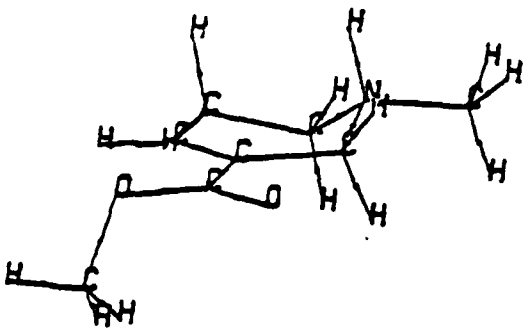


CHART III

GLOBAL MINIMUM STRUCTURES

o. Arecoline (H, CH_3)



p. Arecoline (CH_3,CH_3)

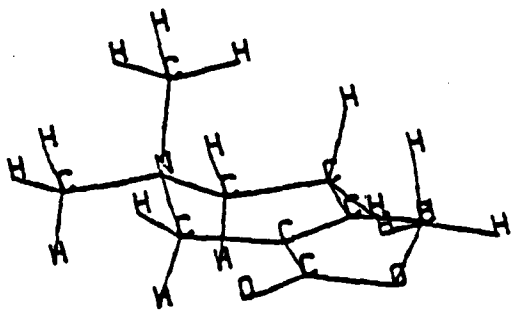


Table I

MM2 Calculated - Global Minimum Structures

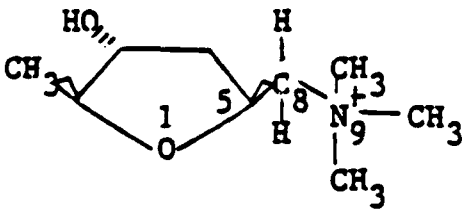
Agonist	[a]Steric Energy	Degree of Dihedral Angle 1,5,8,9	[b]Non-Bonded Dist. Between N···O (A°)
Muscarine	27.71	73.25	3.064
Epiallomuscarine	27.90	70.00	3.046
Epimuscarine	27.31	65	2.998
Allomuscarine	28.49	65	3.047
Dehydromuscarine(cis)	12.89	75.35	3.527
Dehydromuscarine (trans)	13.29	69.46	3.415
Muscarone(cis)	31.14	72.25	3.125
Muscarone(trans)	31.85	-72.82	3.108
F2268(cis)	22.61	70.35	3.115
F2268(trans)	22.68	-73.18	3.133
5-methylfurmethide	4.94	72.3	3.589
TFTM	25.74	71.38	3.047
F2581	33.08	diequatorial	5.13
Arecoline (H,H)	-15.13	180	5.761
Arecoline (H, CH_3)	-13.05	180	5.621
Arecoline (CH_3,CH_3)	- 8.09	180	5.823

[a]Units - kilocalories/mole

[b]N...O - distances calculated by adding 1.74Å to the ether oxygen by the method described in the text.

TABLE II - Muscarine-

MM2 Calculations Dihedral Angle vs Steric Energy and Non-Bonding Distance

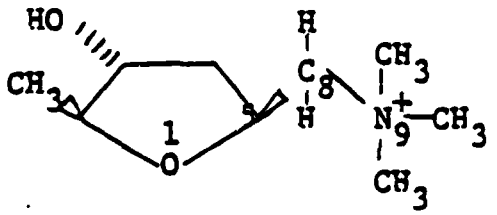


Degree of Dihedral Angle 1-5-8-9	Steric Energy	Non-Bonded Dist. Betw. $\overset{+}{N}$&O (without adding 1.74)	Non-Bonded Dist. Betw. $\overset{+}{N}$&O (adding 1.74)	
0^{o}	32.0992	2.881	2.589	
30^{o}	30.1730	2.928	2.625	
60^{o}	27.9962	3.082	2.931	
90^{o}	28.4646	3.294	3.384	
120^{o}	30.6470	3.561	3.921	
*150^{o}	30.0632	3.745	4.291	
*180^{o}	30.3956	3.801	4.405	
210^{o}	37.9842	3.738	4.358	
240^{o}	51.0647	3.561	4.096	
270^{o}	36.3006	3.314	3.501	
300^{o}	37.119	3.037	2.943	
330^{o}	-	-	-	
360^{o}	32.1006	2.882	2.588	
**73.25^{o}	27.71	3.144	3.064	Global Minimum

*Beers and Reich distance can be achieved within a resonable (< 5kcal) energy difference from the global minimum.

TABLE III - Epiallo muscarine

MM2 Calculations Dihedral Angle versus Steric Energy and N....O Nonbonded Distance

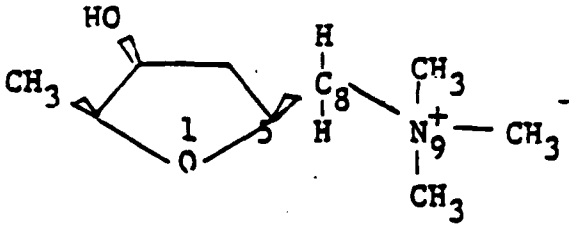


Angle	Steric Energy	Non-Bonded Dist. Betw. $\overset{+}{N}$&O	Adding 1.74	
0°	32.5077	2.887	2.754	
30°	30.2524	2.936	2.717	
60°	28.1305	3.086	2.928	
90°	28.7245	3.296	3.349	
120°	30.8554	3.564	3.899	
*150°	30.2598	3.744	4.278	
*180°	30.5754	3.806	4.477	
210	40.5153	3.743	4.496	
240	49.8966	3.566	4.298	
270	35.1314	3.305	3.610	
300	36.1160	3.026	3.052	
330	-	-	-	
360	32.5109	2.889	2.700	
70°	27.8961	3.145	3.046	-Global Minimum

*Beers and Reich distance can be achieved within a reasonable (0.5kcal.) energy difference from the global minimum.

TABLE IV - Epimuscarine MM_2 Calculations

Dihedral Angle Versus Steric Energy and Nonbonded N---O Distance

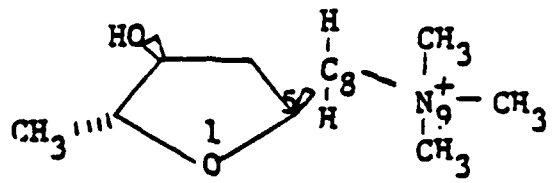


Angle	Steric Energy	Non-Bonded Dist. Betw. $\overset{+}{N}$&O	Adding 1.74	
0^0	31.47	2.877	2.800	
30^0	28.9260	2.910	2.798	
60^0	27.3719	3.055	2.947	
90^0	28.4111	3.266	3.369	
120^0	30.4002	3.542	3.937	
*150^0	29.5390	3.729	4.315	
*180^0	31.0881	3.806	4.426	
210^0	54.6888	3.744	4.382	
240^0	57.0296	3.568	4.124	
270^0	37.8808	3.293	3.538	
300^0	36.2178	3.015	2.986	
330^0	42.1248	2.790	2.472	
360^0	31.3326	2.869	2.695	
** 65^0	27.3140	3.084	2.998	- Global Minimum

*Beers and Reich distance can be achieved within a reasonable (5kcal) energy difference from the global minimum.

TABLE V - Allomuscarine MM2 Calculations

Dihedral Angle Versus Steric Energy and N····O Nonbonded Distance



Angle	Steric Energy	Dist. (without adding 1.74	Adding 1.74
0°	33.0342	2.896	3.053
30°	30.0768	2.916	2.949
60°	28.4934	3.059	3.025
90°	29.0921	3.285	3.632
*120°	31.1177	3.556	4.136
*150°	30.7894	3.739	4.526
*180°	32.7963	3.812	4.812
210°	44.5254	3.751	4.916
240°	-	-	-
270°	51.3878	3.625	4.852
300°	54.4142	3.413	4.481
330°	-	-	-
360°	32.5591	2.868	2.743
** 65°	28.4932	3.088	3.047 (Global Minimum

* Beers and Reich distance can be achieved within a reasonable (<5kcal.) energy difference from the global minimum.

TABLE VI

DEHYDRO-MUSCARINE (CIS) - DIHEDRAL DRIVER CALCULATIONS

ANGLE	STERIC ENERGY	NON-BONDED BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	16.8362	3.011	2.982
30	15.3340	3.048	3.008
60	13.3445	3.175	3.301
90	13.8236	3.385	3.779
*120	17.2516	3.611	4.205
*150	19.0228	3.783	4.526
*180	18.9680	3.839	4.679
210	21.8192	3.784	4.642
240	19.5610	3.627	4.399
*270	14.9363	3.396	4.018
300	15.2707	3.162	3.500
330	-	-	-
360	16.6017	3.008	2.991
GLOBAL MINIMUM			
75.35	12.9871	3.269	3.527

*Beers and Reich N...O distance can be achieved within a reasonable energy difference from the global minimum.

TABLE VII

DEHYDRO-MUSCARINE (TRANS)- DIHEDRAL DRIVER CALCULATIONS

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	16.7992	3.011	3.030
30	15.4710	3.050	3.042
60	13.4395	3.177	3.302
90	13.6632	3.375	3.753
*120	16.9415	3.610	4.195
*150	18.6415	3.784	4.527
*180	18.5633	3.838	4.677
210	21.3898	3.783	4.641
240	19.4275	3.626	4.399
270	14.7920	3.332	3.922
300	15.7969	3.079	3.379
330	-	-	-
360	16.5426	3.007	2.998
GLOBAL MINIMUM			
69.46	13.2904	3.223	3.415

*Beers and Reich N...O distance can be achieved within a reasonable energy difference from the global minimum.

TABLE VIII

MUSCARONE(CIS) (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	35.4632	2.883	2.579
30	33.5596	2.938	2.648
60	31.3711	3.089	2.960
90	32.0099	3.304	3.414
*120	34.3315	3.570	3.945
*150	33.4717	3.750	4.304
*180	33.3810	3.813	4.431
210	46.5779	3.750	4.381
240	56.0390	3.573	4.116
270	39.4803	3.321	3.512
300	40.1041	3.045	2.956
330	-	-	-
360	35.4635	2.886	2.584
GLOBAL MINIMUM			
72.254	31.1444	3.166	3.125

*Beers and Reich N...O distance can be achieved within a resonable energy from the global minimum

TABLE IX

MUSCARONE(TRANS) (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	36.9340	2.866	2.590
30	35.9857	2.945	2.851
60	35.9474	3.127	3.578
90	39.4441	3.397	4.269
120	42.6102	3.654	4.958
150	39.0393	3.784	5.028
180	37.7577	3.826	4.941
210	39.2353	3.764	4.667
240	40.8118	3.589	4.271
270	38.3541	3.335	3.841
300	37.8082	3.061	3.497
330	55.1198	2.844	3.371
360	36.8031	2.876	2.597
GLOBAL MINIMUM			
-72.817	31.8475	3.171	3.108

TABLE X

F2268(CIS) (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	26.7321	2.882	2.657
30	25.1673	2.934	2.684
60	22.9113	3.085	2.984
90	23.3569	3.297	3.430
*120	25.8362	3.560	3.957
*150	25.2501	3.740	4.338
*180	25.0284	3.800	4.467
210	36.5119	3.737	4.429
240	52.2328	3.561	4.175
270	30.7114	3.288	3.542
300	31.5263	3.008	2.980
330	36.2617	2.782	2.480
360	26.7295	2.884	2.653
GLOBAL MINIMUM			
70.350	22.6097	3.146	3.115

*Beers and Reich distance can be achieved within a reasonable energy difference from the global minimum.

TABLE XI

F2268(TRANS) (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (WITHOUT ADDING 1.74)	(ADDING 1.74)
0	27.0962	2.886	2.742
30	26.3905	2.954	3.035
60	27.8748	3.155	3.491
90	28.8113	3.374	3.847
120	31.9911	3.624	4.244
150	28.7478	3.770	4.439
*180	25.2976	3.803	4.484
*210	26.8101	3.739	4.273
240	27.5736	3.562	3.875
270	23.4769	3.296	3.395
300	24.5012	3.013	2.858
330	33.2217	2.788	2.506
360	27.1035	2.887	2.756
GLOBAL MINIMUM			
-73.183	22.6839	3.168	3.133

*Beers and Reich distance can be achieved within a reasonable energy difference from the global minimum.

TABLE XII

5-METHYLFURMETHIDE - DIHEDRAL ANGLE DRIVER CALCULATIONS

(O-C-C-N) ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)
0	7.8054	2.903
30	6.8470	3.042
60	5.2360	3.407
90	5.1620	3.868
*120	7.8222	4.288
*150	9.6616	4.555
*180	9.6294	4.634
*210	9.6615	4.554
*240	7.8221	4.287
270	5.1619	3.867
300	5.2378	3.407
330	6.8467	3.042
360	7.8052	2.901
GLOBAL MINIMUM		
72.3	4.9423	3.589

*Beers and Reich distance can be achieved within a reasonble energy difference from the global minimum.

TABLE XIII

TFTM - DIHEDRAL ANGLE DRIVER CALCULATIONS

(O-C-C-N) ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)
0	29.9969	2.673
30	28.0292	2.682
60	25.9540	2.911
90	26.5745	3.346
120	28.8811	3.893
* 150	28.3165	4.274
* 180	28.5027	4.455
210	31.9607	4.333
240	34.9764	4.214
270	31.4737	3.775
300	30.4913	3.488
330	29.1929	2.974
360	29.9960	3.047
GLOBAL MINIMUM		
71.38	25.7355	3.047

*Beers and Reich distance can be achieved within a reasonable energy difference from the global minimum.

TABLE XIV

F - 2581 - MM_2 Calculations

	STERIC ENERGY	NON-BONDED DIST. BETW. N^+ & O (ADDING 1.74)
E^*	33.0837	5.131
A^*	**	3.667

* E : EQUATORIAL, A : AXIAL expressed in bond $C-N^+$

** The conformer A is transformed to conformer E after minimization by MM2

TABLE XV

ARECOLINE (H, H) -DIHEDRAL ANGLE DRIVER CALCULATIONS

ANGLE (x)	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)	
* 0	- 7.3232	4.439	S-CIS
* 30	- 7.6732	4.455	
* 60	- 7.6363	4.641	
90	- 8.4700	4.805	
120	-11.6448	5.058	
150	-14.2788	5.404	
* * 180	-15.1262	5.761	S-TRANS
210	-14.0699	6.041	
240	-10.8724	5.930	
270	- 7.1244	5.093	
300	- 6.6777	4.721	
330	- 6.9701	4.520	
360	- 7.3223	4.437	

* * GLOBAL MINIMUM

---

*Beers and Reich distance can be achieved within a reasonable energy difference from the global minimum.

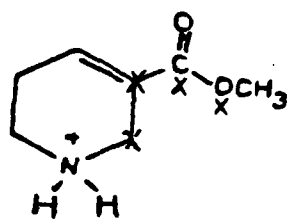


TABLE XVI

ARECOLINE (H, CH3) - DIHEDRAL ANGLE DRIVER CALCULATIONS

	ANGLE(x)	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)	
	0	- 5.2516	4.538	S-CIS
	30	- 5.1769	4.482	
	60	- 5.0884	4.471	
	90	- 5.7944	4.474	
	120	- 9.2410	4.689	
	150	-12.1585	5.138	
**	180	-13.0450	5.621	S-TRANS
	210	-12.0999	5.997	
	240	- 9.3215	6.026	
	270	- 5.9268	5.495	
	300	- 5.2402	5.051	
	330	- 5.3669	4.693	
	360	- 5.2513	4.540	

** GLOBAL MINIMUM

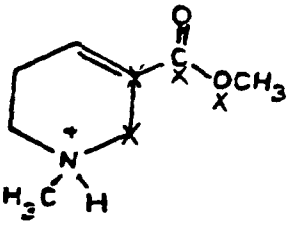


TABLE XVII

ARECOLINE (CH3, CH3) - DIHEDRAL ANGLE DRIVER CALCULATIONS

ANGLE(x)	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)	
0	-0.6485	4.452	S-CIS
30	-1.1694	4.486	
60	-1.1235	4.688	
90	-2.0598	4.862	
120	-4.9738	5.134	
150	-7.3248	5.482	
* *180	-8.0919	5.823	S-TRANS
210	-7.1987	6.096	
240	-4.2426	5.973	
270	-0.3862	5.032	
300	0.0060	4.640	
330	-0.2453	4.502	
360	-0.6466	4.451	

** GLOBAL MINIMUM

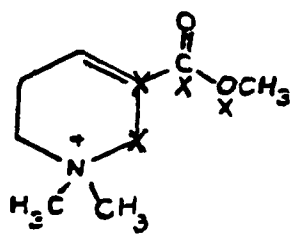


TABLE XVIII

DECALINE DERIVATIVES - Minimized by MM2 Calculations

CONFORMER	(C-C-O-C) ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N^+ & O (ADDING 1.74)
E/E*	98	27.3290	3.518
A/E*	150	32.4259	3.683

* E : Equatorial, A : Axial expressed in bonds $C-N^+$ & C-C

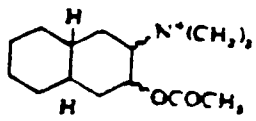


TABLE XIX

DECALINE DERIVATIVES -- MINIMIZED BY MOPAC MNDO

CONFORMER	(KCAL/MOL) HEAT FORMATION	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)
A/A	99.33	4.090
E/E	92.83	3.172
A/E	97.36	3.262
E/A	97.51	2.414

CONFORMER DENOTED BY N+(CH3)3/OCOCH3

A : AXIAL
E : EQUATORIAL

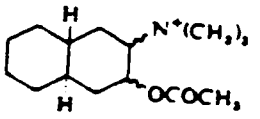


CHART IV

Trans Decalin Diequatorial Derivative

MNDO Optimized Structure

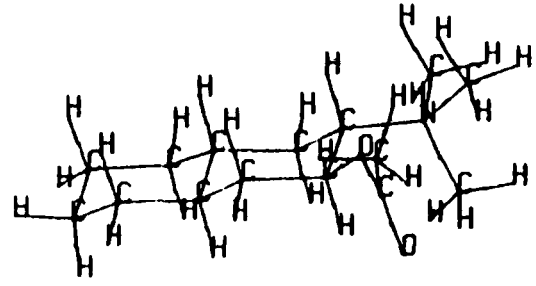


CHART IV

Trans Decalin Diaxial Derivative

MNDO Otimized Structure

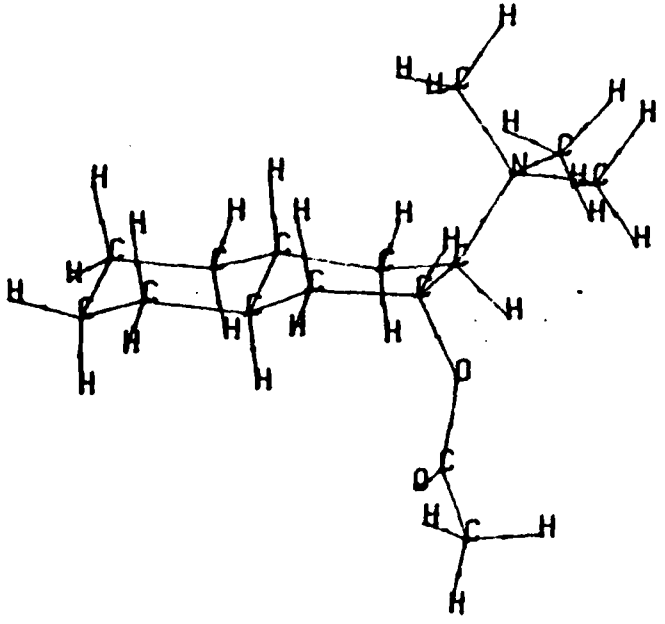


CHART IV

Trans Decalin Equatorial(N) Axial(O) Derivative

MNDO Optimized Structure

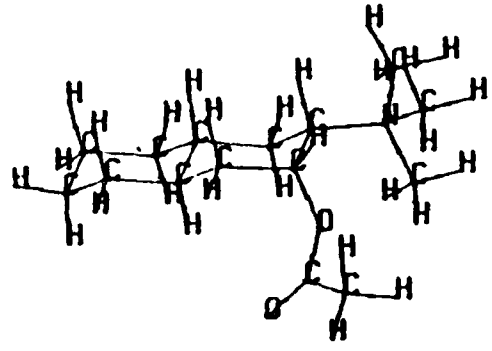
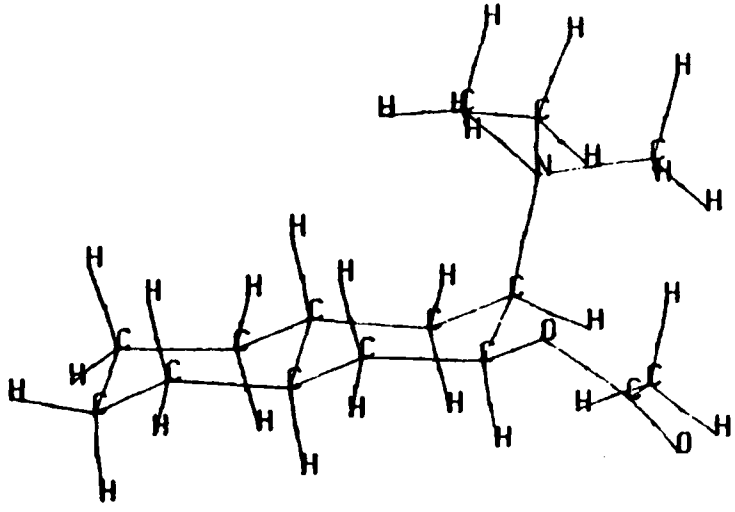


CHART IV

Trans Decalin Axial(N) Equatorial(O) Derivative

MNDO Optimized Structure



PILOCARPINE

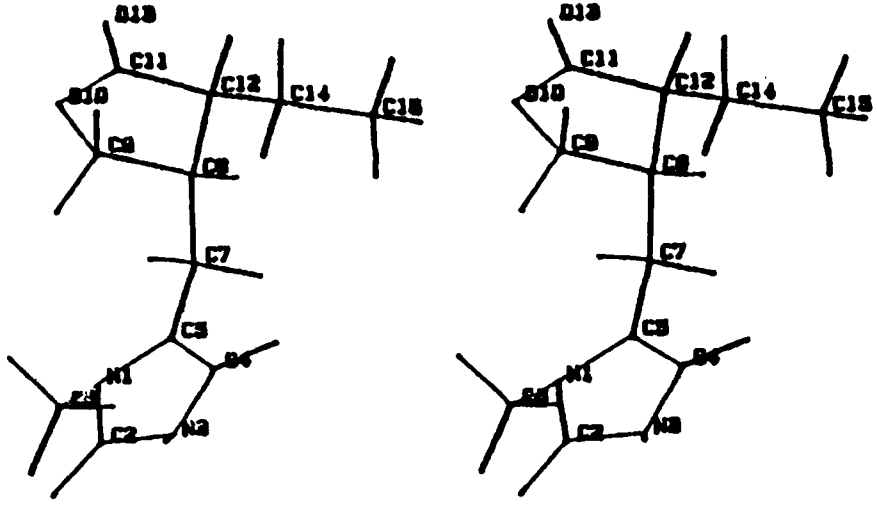


CHART VI

PILOCARPINE - rotatable bonds

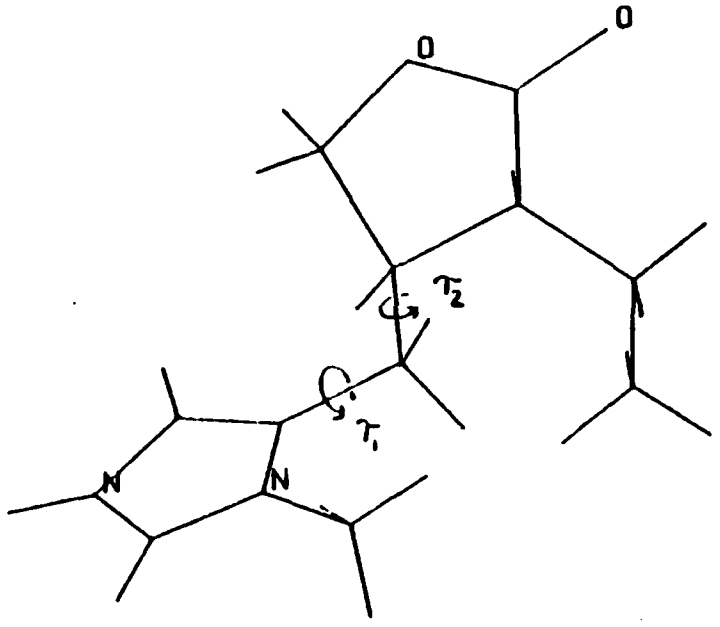


TABLE XX

MM2 Minimization of Pilocarpine #1, #2, and #3 Conformations

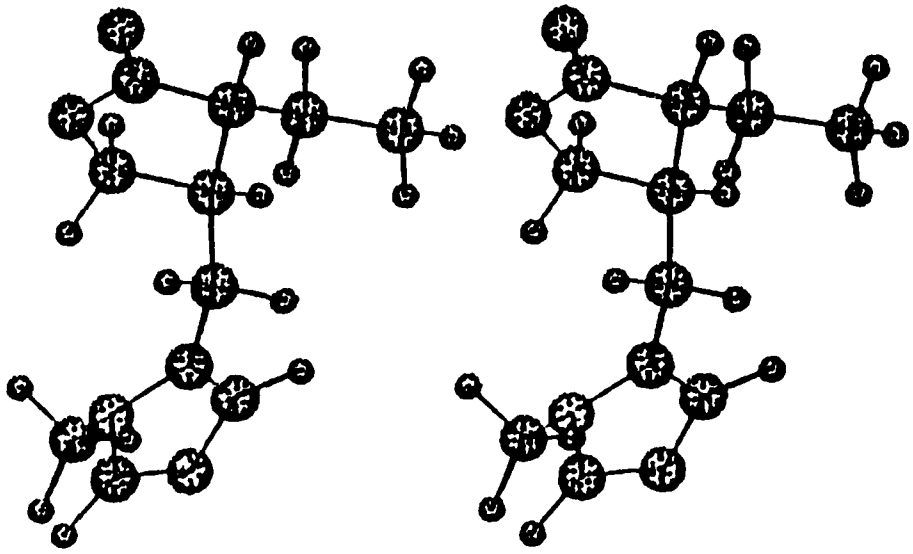
Structure	Tau1	Tau2	Energy (kcal/mole)*
1	65.7	64.7	0.00
2	68.1	-61.1	3.16
3	121.2	160.0	1.92
4	-57.3	167.2	1.22
x-ray	7.4	72.0	3.15

*Energies are relative to one another.

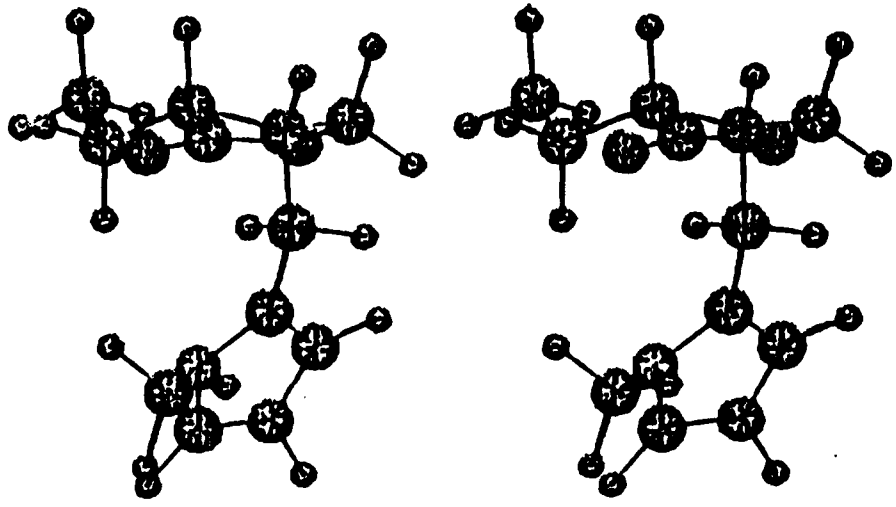
Structure 1 (Pilocarpine#1) is the global minimum and closest to the x-ray structure. Structures 1 and 2 (Pilocarpine #1 and #2) have Beers and Reich NO distances. We are checking further into the conformations of pilocarpine to see if we can derive one that fits the four parameter criteria better. Pilocarpine is a weak agonist and being that it does not fit the bioactive criteria could account for its weak potency.

CHART VII

PILOCARPINE I



PILOCARPINE 2



PILOCARPINE 3

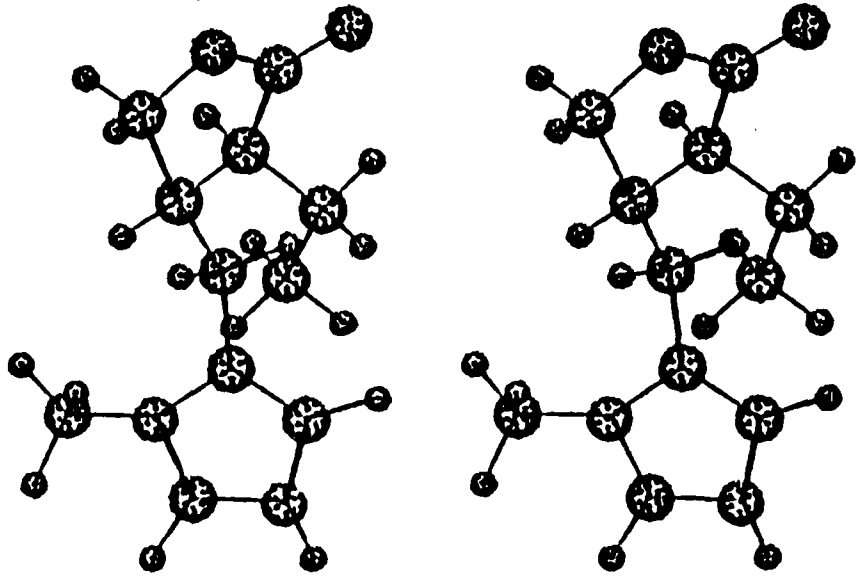


CHART VII

PILOCARPINE 4

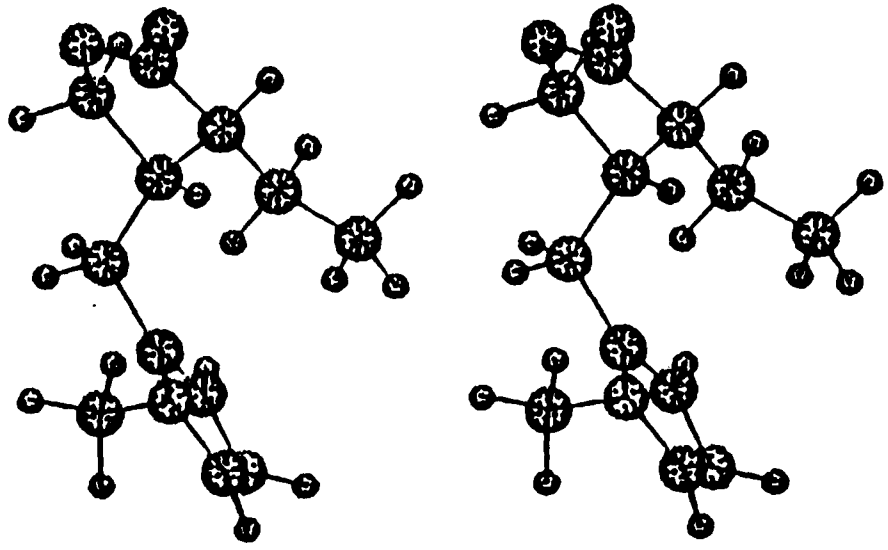


CHART VIII

PILOCARPINE _X-RAY STRUCTURE

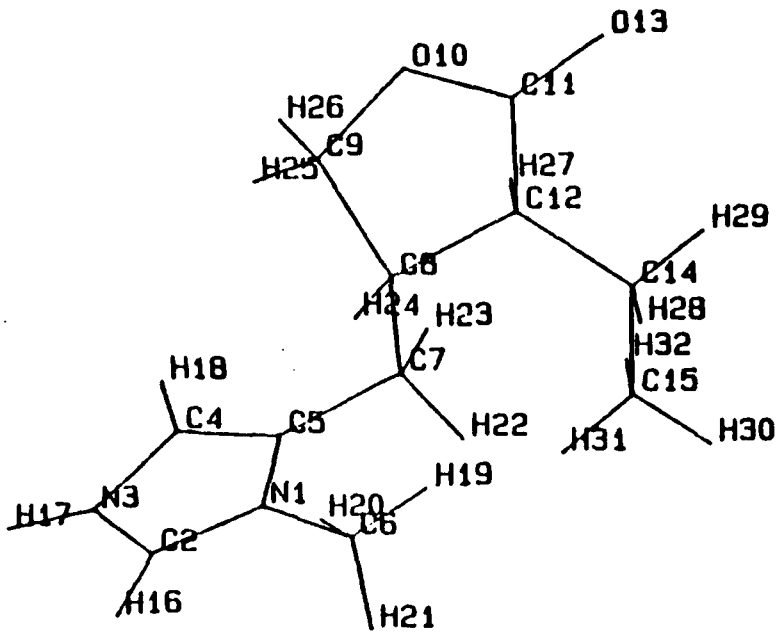


TABLE XXI

MUSCARINIC ANTAGONIST

ATROPINE (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)
0	22.3715	5.363
30	22.0417	5.084
60	21.3413	4.795
90	22.0668	4.575
120	23.4359	4.483
150	23.3998	4.588
180	22.4865	4.848
210	19.3081	3.592
240	17.6841	4.533
270	15.4329	5.168
300	14.7459	5.295
330	20.0323	5.557

TABLE XXII

MUSCARINIC ANTAGONIST

DIBENAMINE (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)
0	95.6743	5.135
30	111.0800	5.100
60	153.0625	4.818
90	135.9192	4.554
120	153.7770	4.509
150	142.1066	4.650
180	147.3234	4.872
210	91.0997	5.155
240	35.2099	5.446
270	48.5030	5.571
300	49.5511	5.600
330	126.9004	5.484
110.8	42.7651	4.445

TABLE XXIII

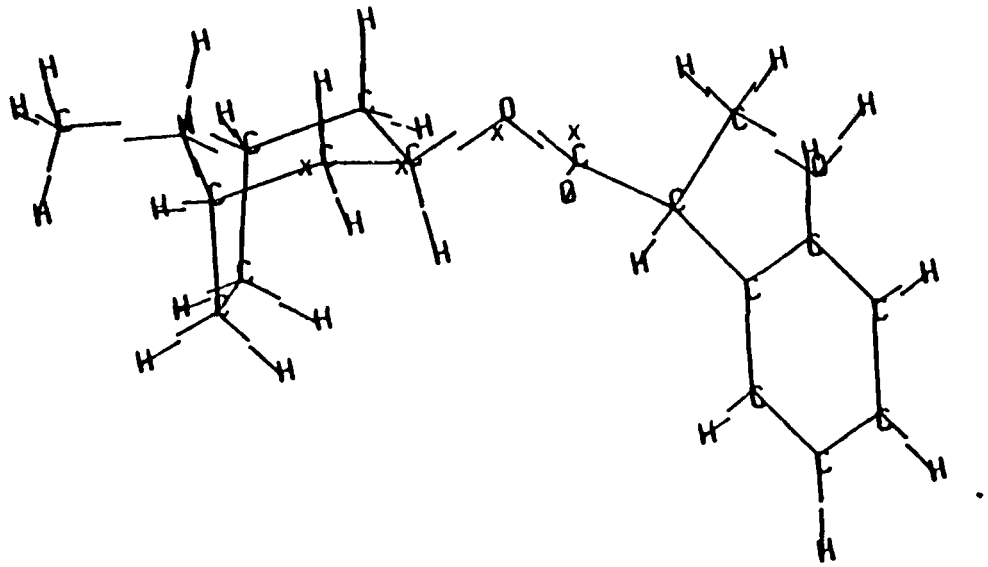
MUSCARINIC ANTAGONIST

QUINUCLIDINE DERIVATIVE (DIHEDRAL ANGLE DRIVER CALCULATION)

ANGLE	STERIC ENERGY	NON-BONDED DIST. BETW. N+ & O (ADDING 1.74)
0	37.2395	4.480
30	36.0394	4.154
60	31.9874	3.982
90	32.4231	3.741
120	31.1383	3.746
150	28.2795	4.108
180	27.8741	4.515
210	30.2962	4.605
240	30.2788	5.013
270	29.6323	5.150
300	36.9081	5.027
330	36.7168	4.816

CHART IX

ATROPINE 90^{o}



*Dihedral angle considered denoted by x.

CHART IX

ATROPINE 120°

CHART IX

ATROPINE 150°

CHART IX

ATROPINE 240°

CHART X

DIBENAMINE 110°

CHART XI

QUINUCLIDINE O^{O}

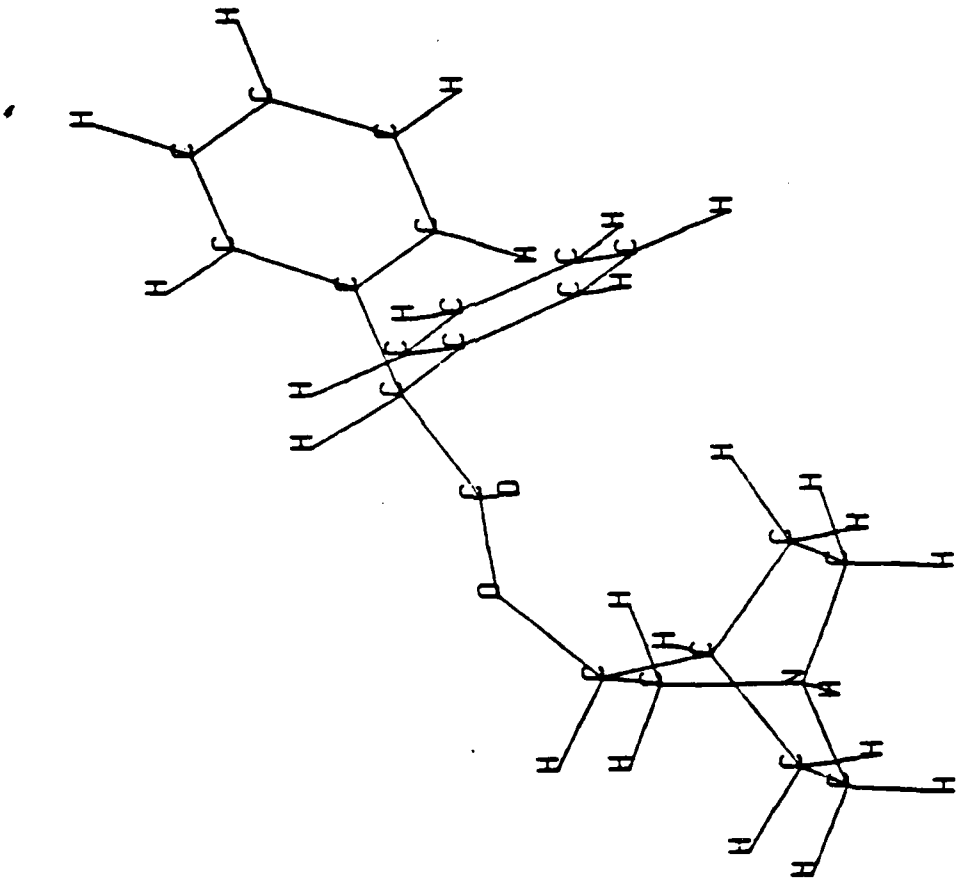


CHART XI

QUINUCLIDINE 180°

FIGURE 5.

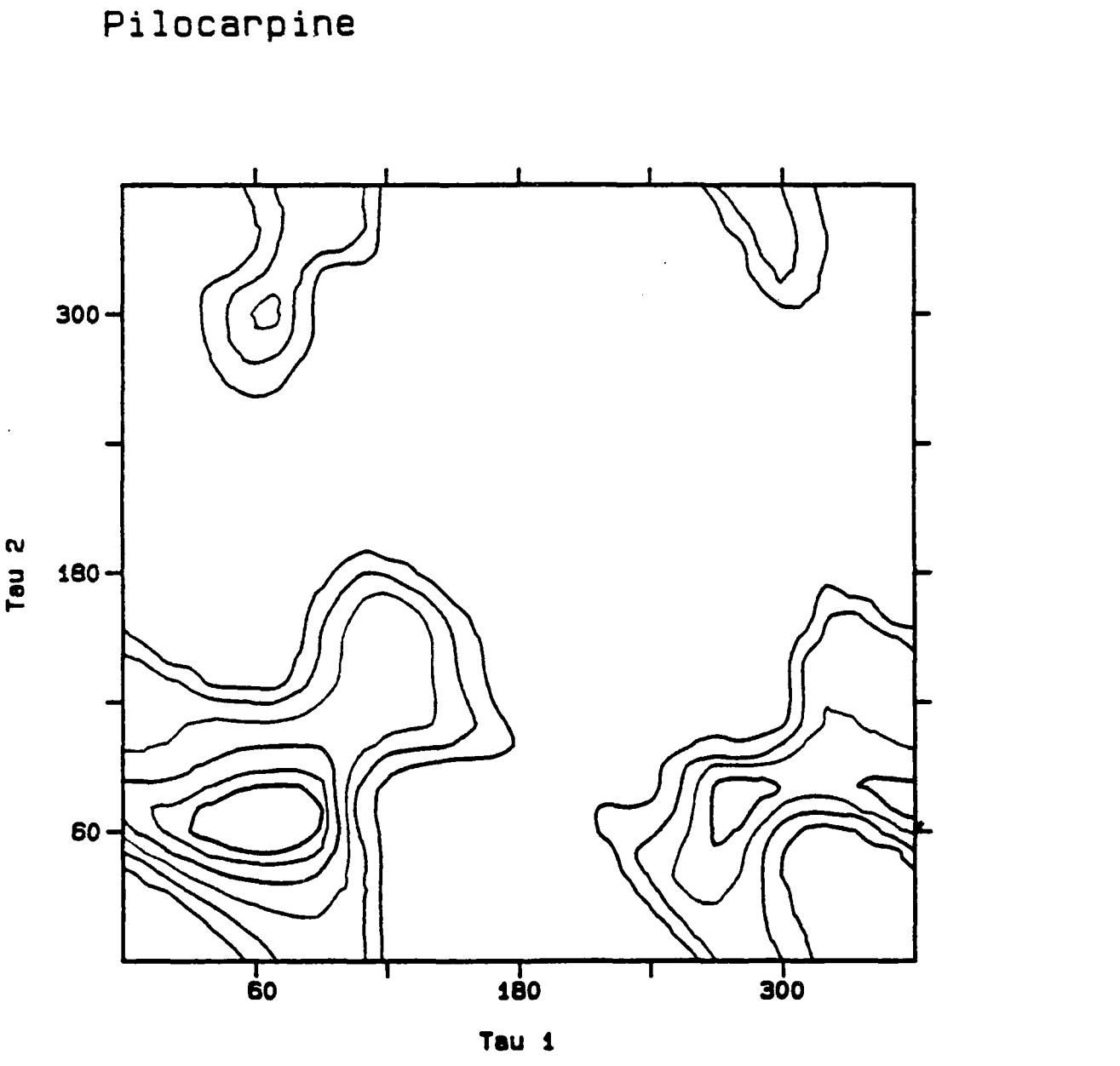
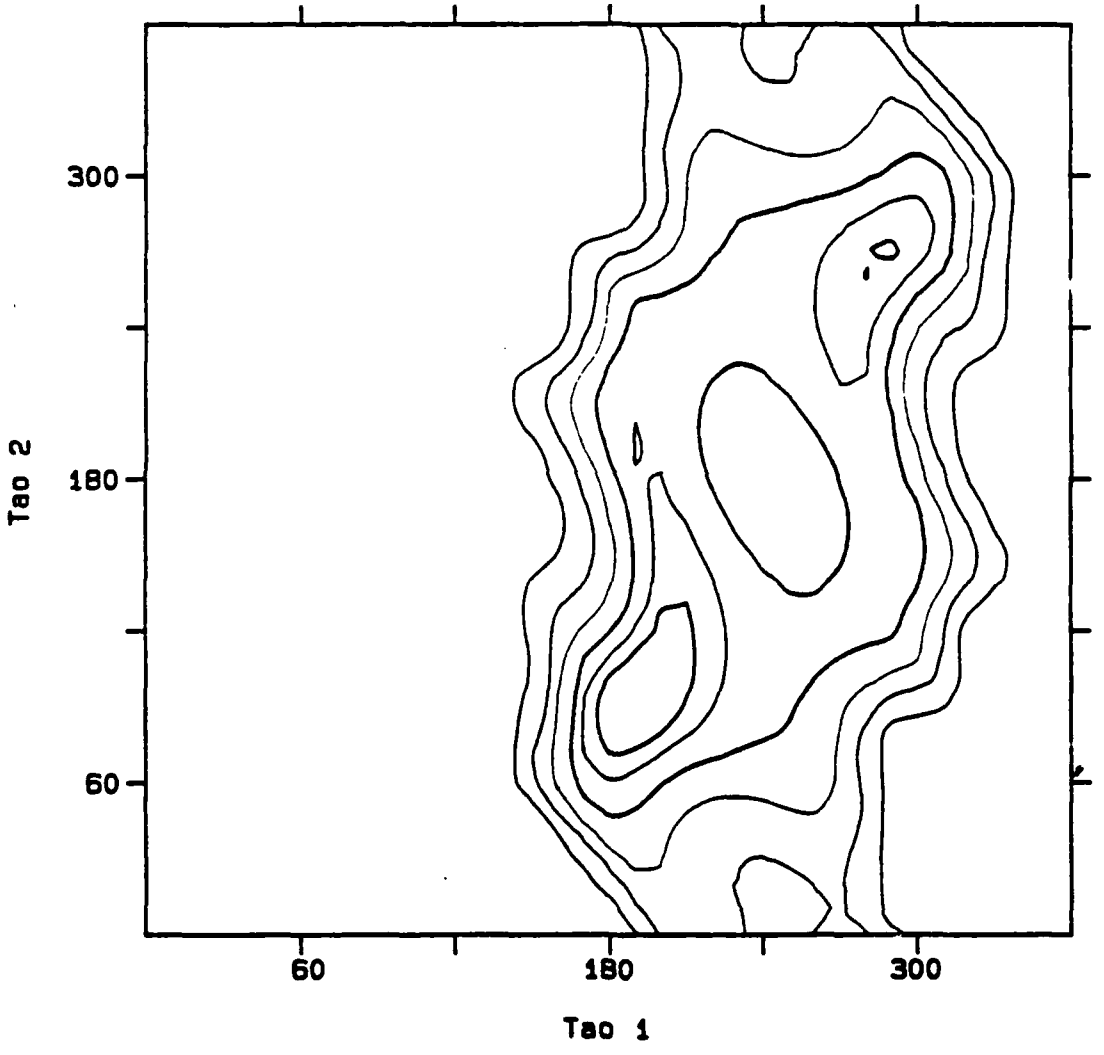

Pilocarpine
300
180
60
Tau 2
60
180
300
Tau 1
1.0 Kcal/Mole
2.0 Kcal/Mole
4.0 Kcal/Mole
8.0 Kcal/Mole
16.0 Kcal/Mole
32.0 Kcal/Mole

FIGURE 6

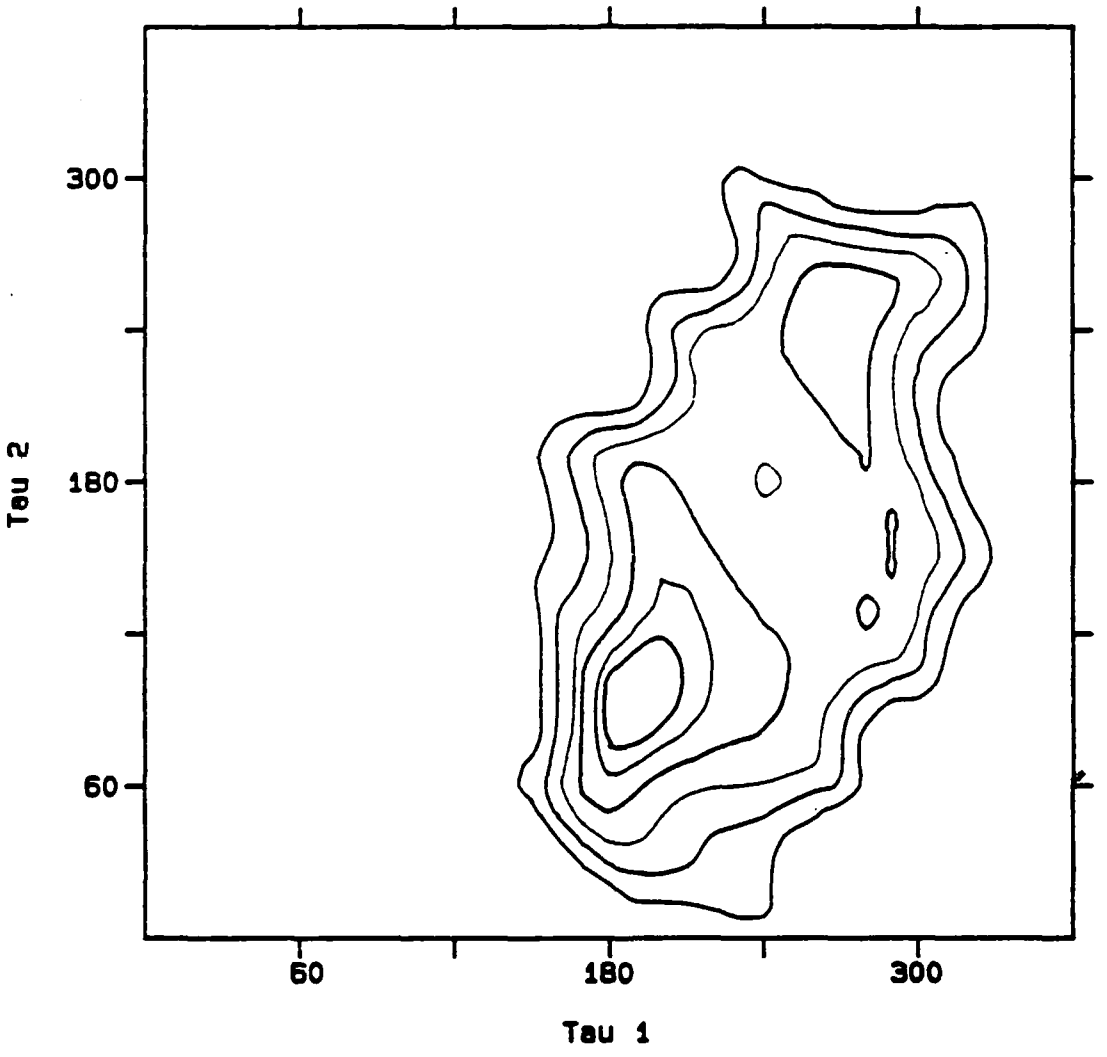
Tropine



1.0 kcal/mole
2.0 kcal/mole
4.0 kcal/mole
8.0 kcal/mole
16.0 kcal/mole
32.0 kcal/mole

FIGURE 7

Atropine-A



1.0 Kcal/Mole
2.0 Kcal/Mole
4.0 Kcal/Mole
8.0 Kcal/Mole
16.0 Kcal/Mole
32.0 Kcal/Mole

FIGURE 7

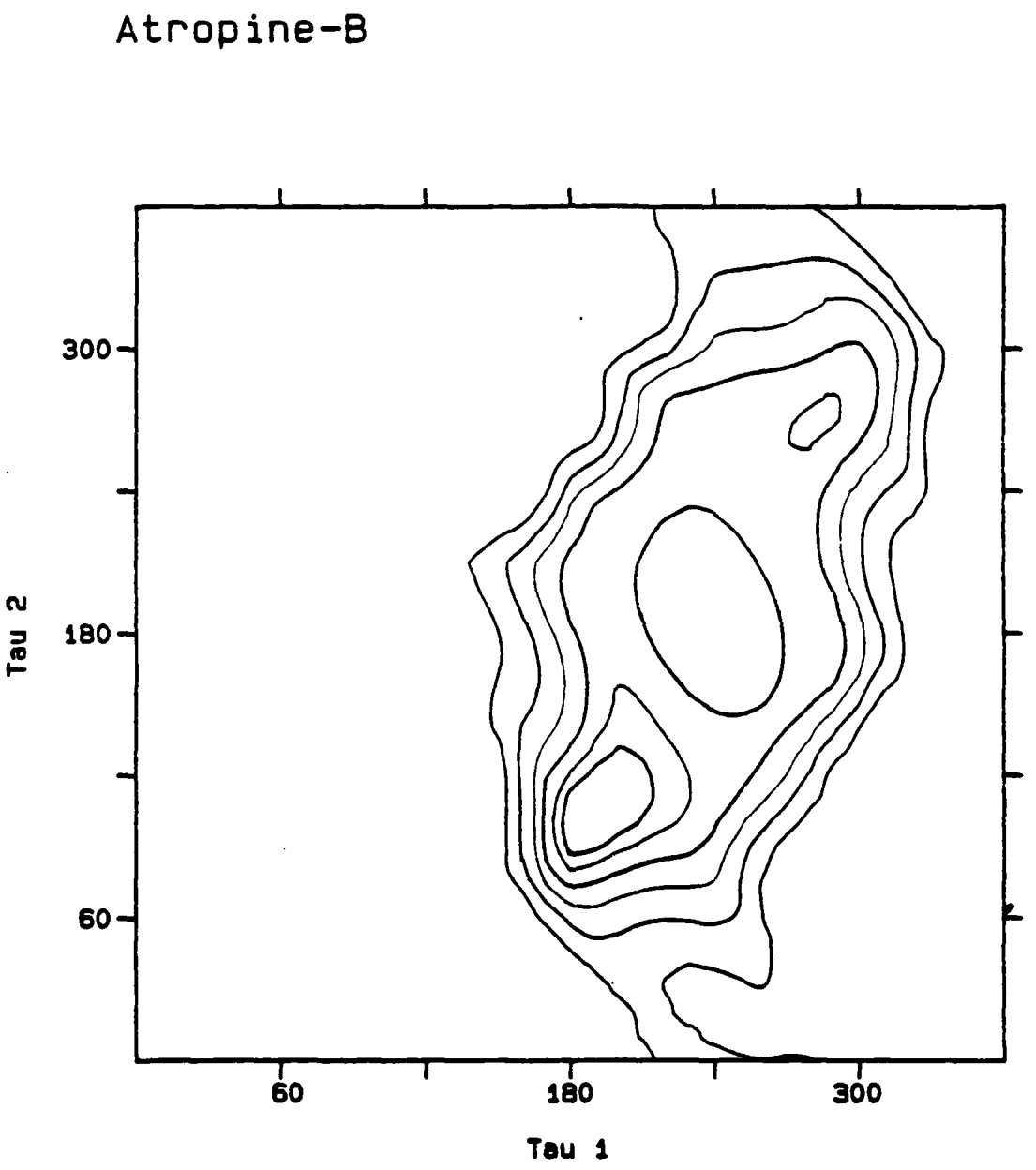
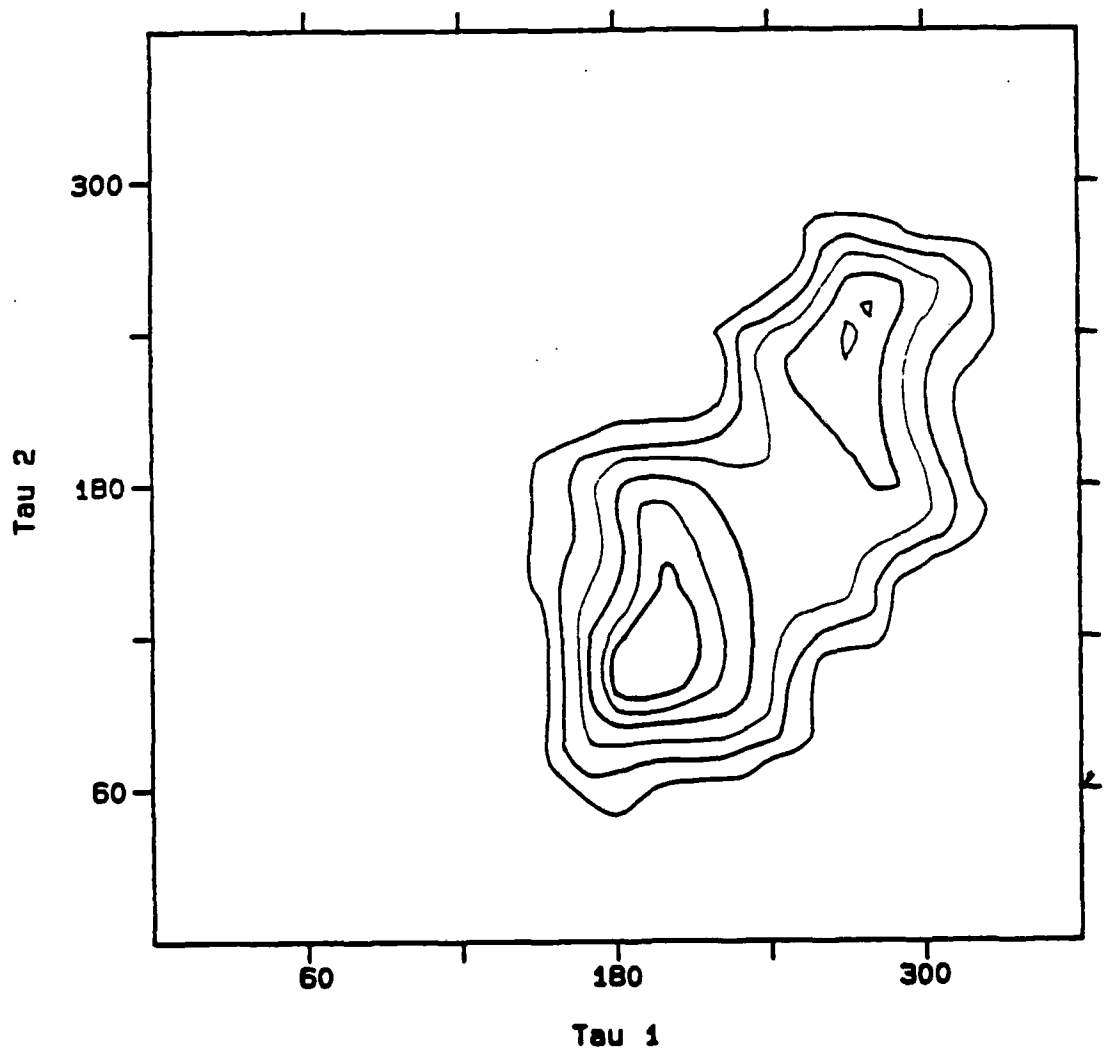

Atropine-B
300
180
60
Tau 2
60
180
300
Tau 1
1.0 Kcal/Mole
2.0 Kcal/Mole
4.0 Kcal/Mole
8.0 Kcal/Mole
16.0 Kcal/Mole
32.0 Kcal/Mole

FIGURE 7



1.0 Kcal/Mole
2.0 Kcal/Mole
4.0 Kcal/Mole
8.0 Kcal/Mole
16.0 Kcal/Mole
32.0 Kcal/Mole

TABLE XXIV

The Two Tropine Minimum Energy Conformations and Geometric Parameters

Conformer	Energy	Tao 1	Tao 2	PQ	PNOQ	Beers
Tropine-A	18.9696	-163.309	96.038	6.691	-35.855	4.155
Tropine-B	18.7607	-67.019	-89.218	6.789	41.566	4.265

Tao 1 = angle C3 C4 O11 C12
Tao 2 = angle C4 O11 C12 C13

Tropine

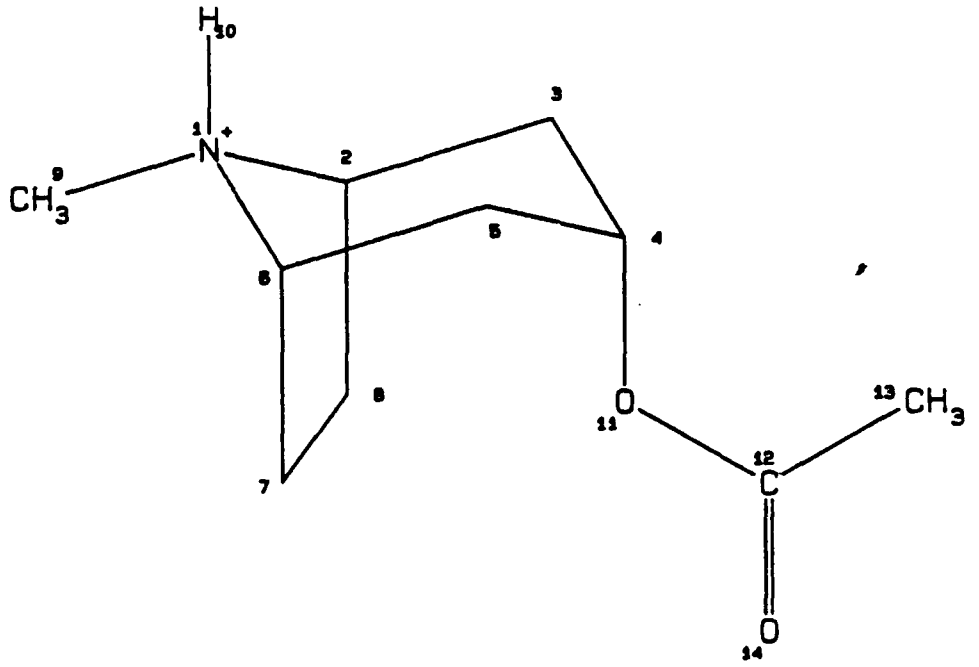
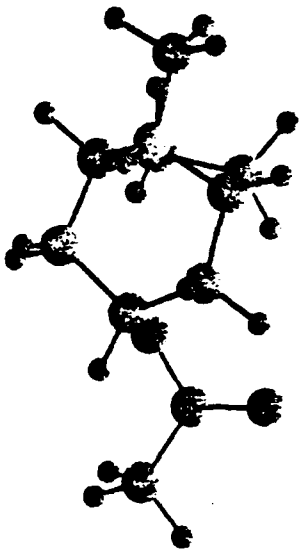
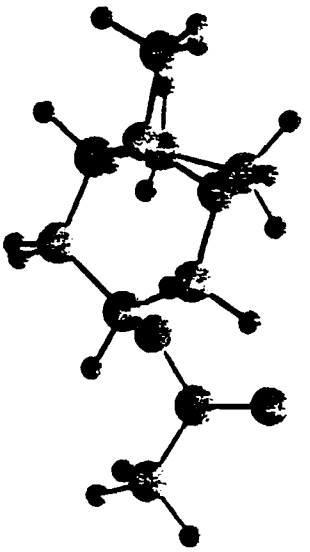
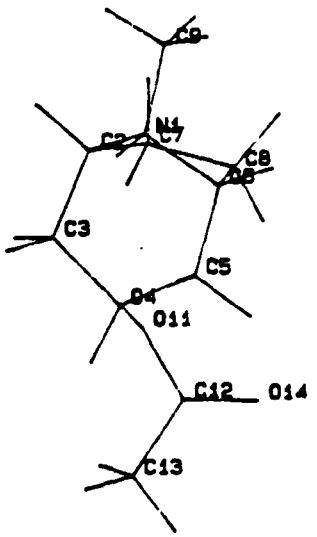


CHART XII

Tropine-A







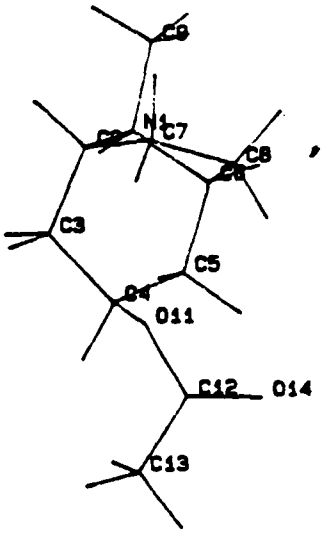


TABLE XXV

The Three Atropine Minimum Energy Conformations and Geometric Parameters

Conformer	Energy	Tau 1	Tau 2	Tau 3	PQ	PNOQ	Beers
Atropine-A	22.6113	-167.461	97.038	62.135	6.701	-39.054	4.174
Atropine-B	19.2504	-168.324	105.262	175.017	6.708	-40.156	4.177
Atropine-C	21.7656	-171.379	105.919	-60.582	6.730	-42.331	4.202

Tau 1 = angle C5 C6 O11 C12
Tau 2 = angle C6 O11 C12 C14
Tau 3 = angle O11 C12 C14 C15

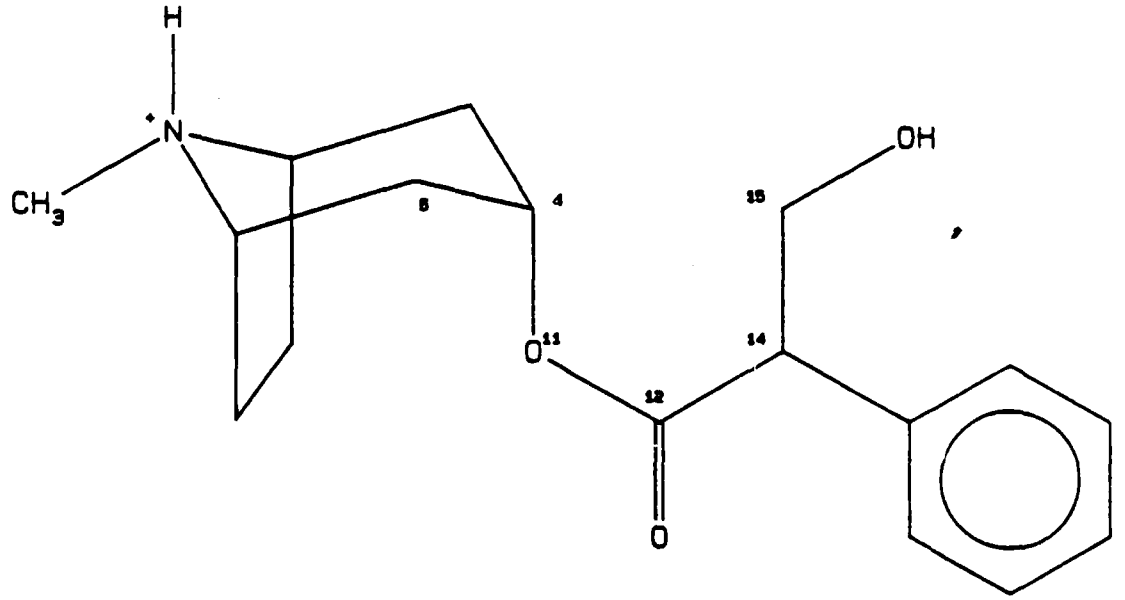
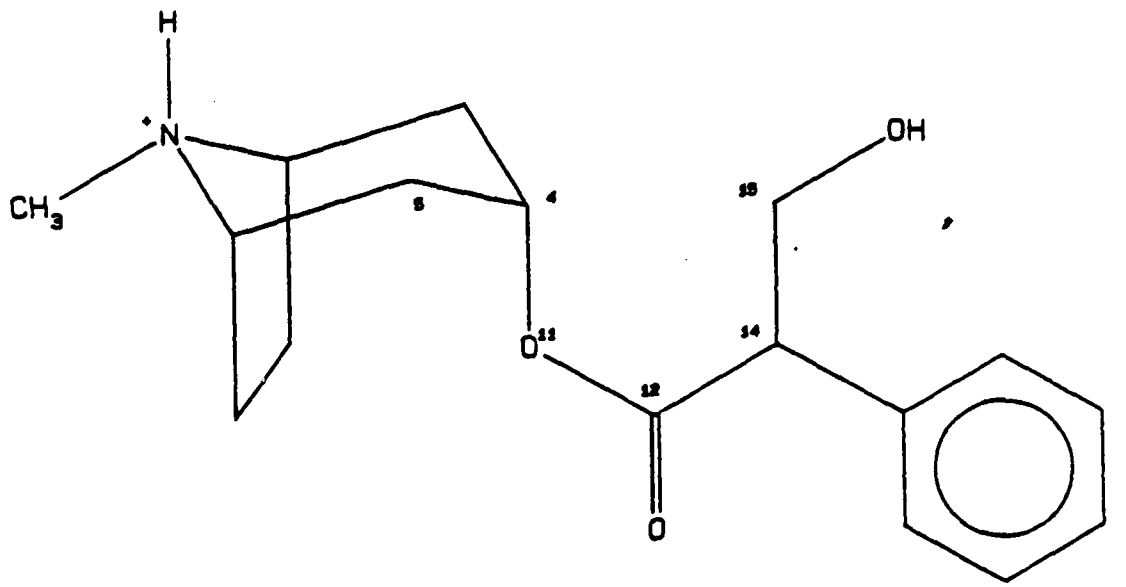


TABLE XXV

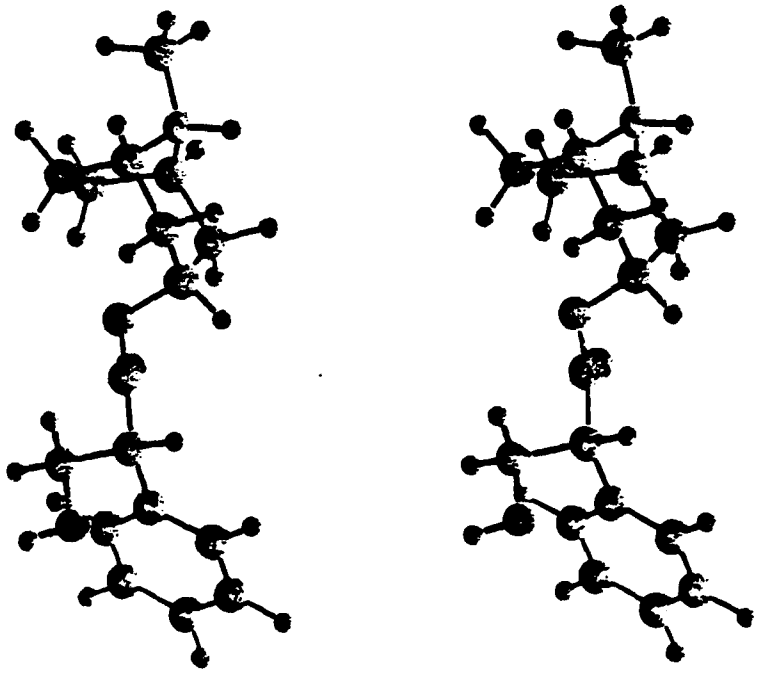
The Three Atropine Minimum Energy Conformations and Geometric Parameters

Conformer	Energy	Tau 1	Tau 2	Tau 3	PQ	PNOQ	Beers
Atropine-A	22.6113	-167.461	97.038	62.135	6.701	-39.054	4.174
Atropine-B	19.2504	-168.324	105.262	175.017	6.708	-40.156	4.177
Atropine-C	21.7656	-171.379	105.919	-60.582	6.730	-42.331	4.202

Tau 1 = angle C5 C6 O11 C12
Tau 2 = angle C6 O11 C12 C14
Tau 3 = angle O11 C12 C14 C15



Atropine-A



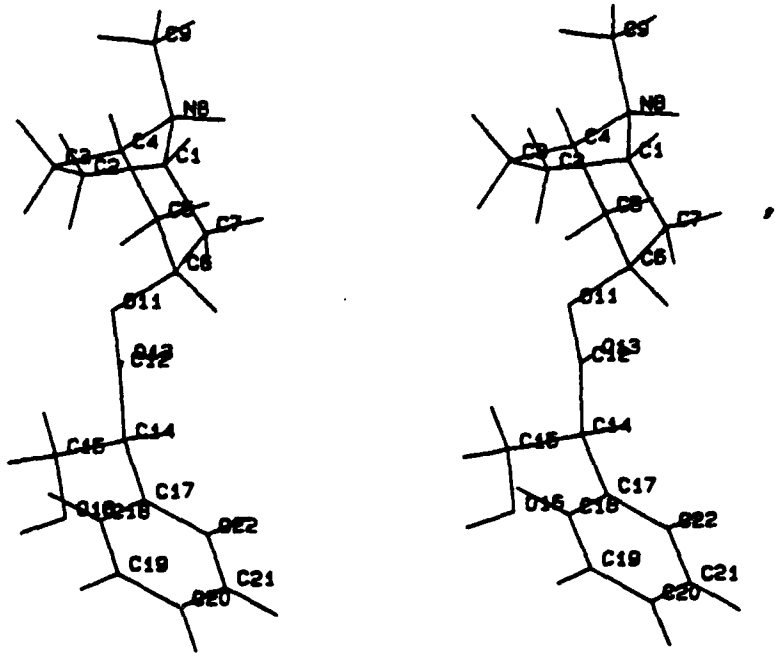
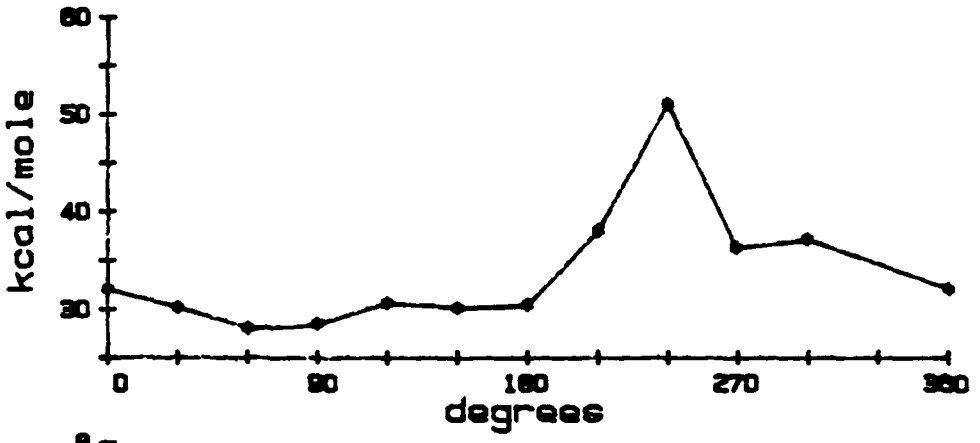


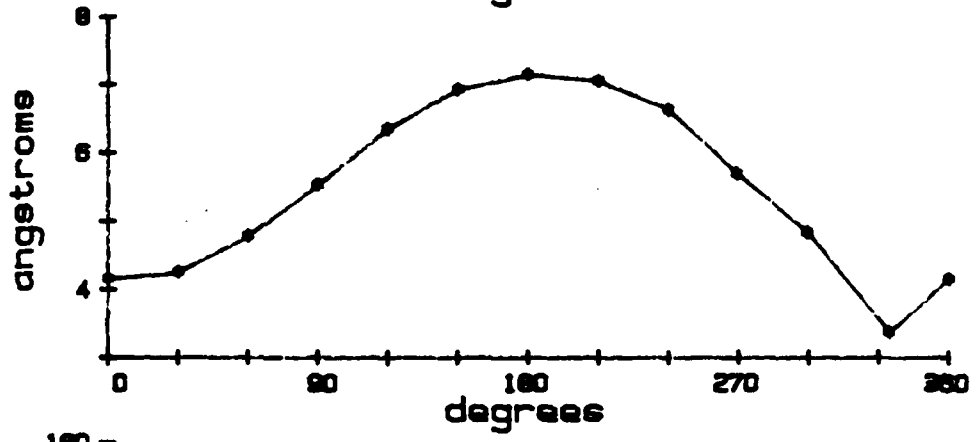
FIGURE 8

MUSCARINE

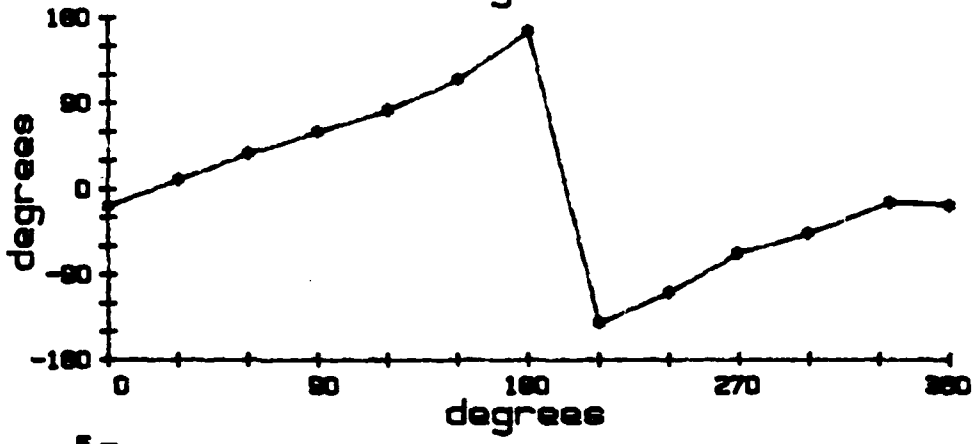
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PQ DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOQ ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

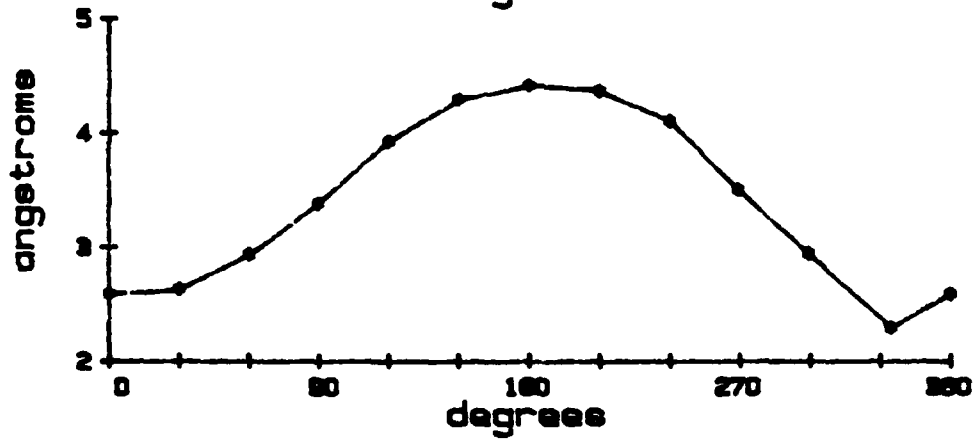
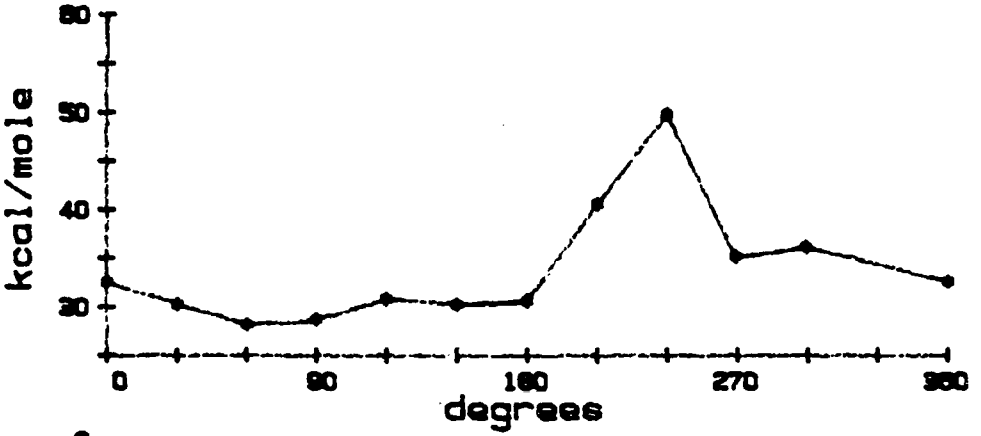


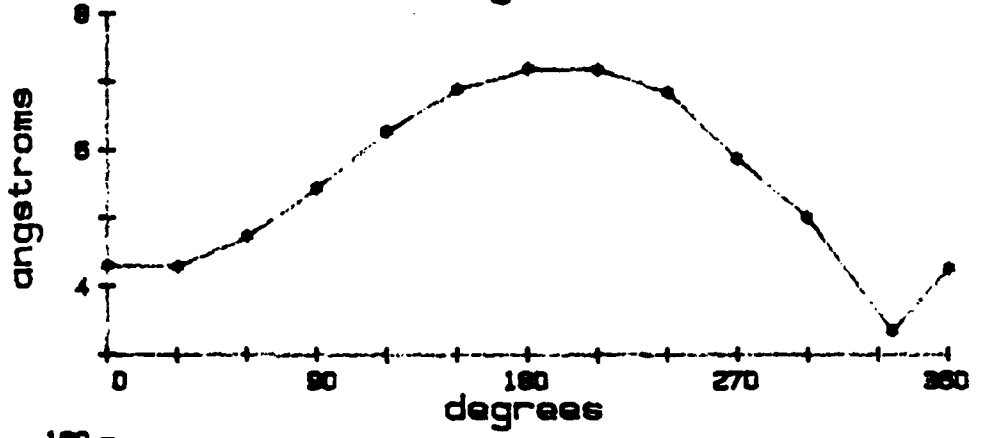
FIGURE 9

EPIALLOMUSCARINE

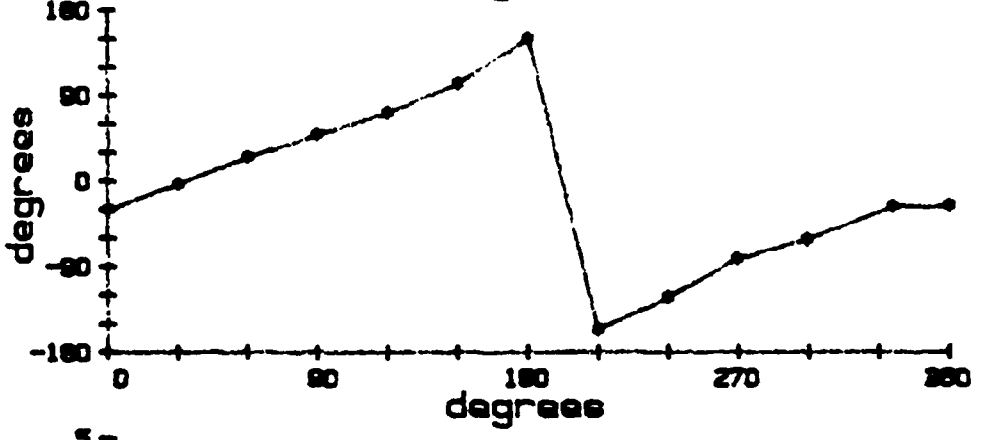
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PO DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOO ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

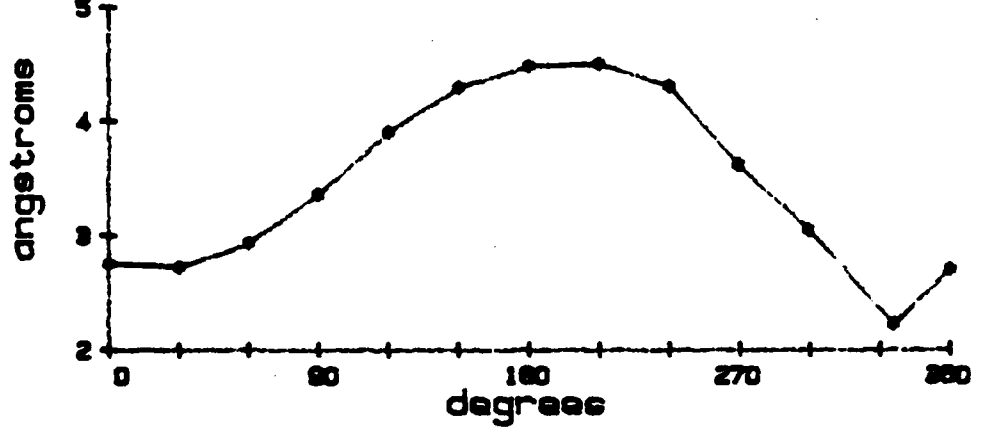
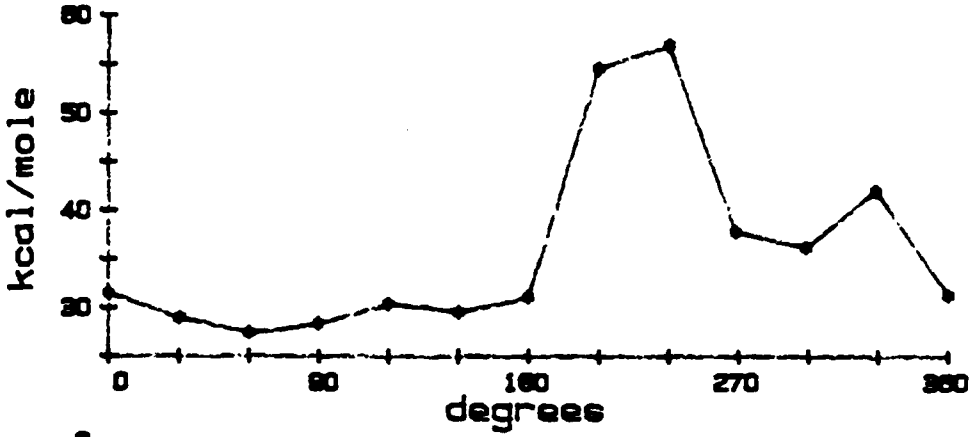


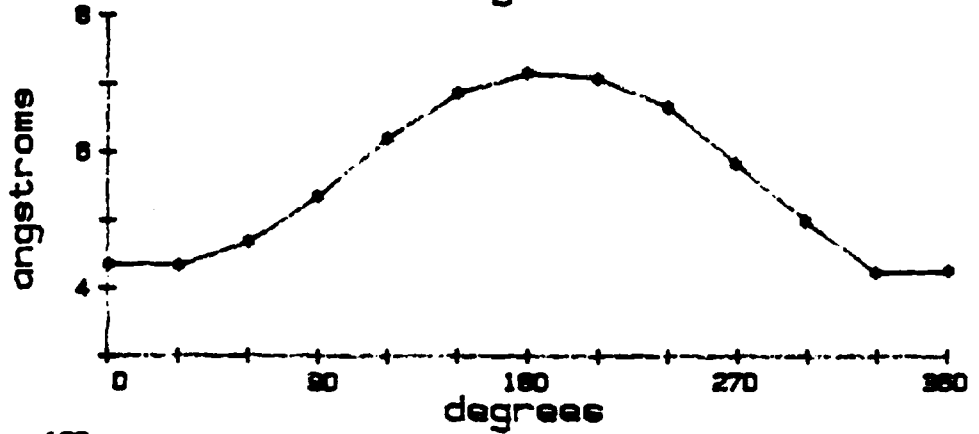
FIGURE 10

EPIMUSCARINE

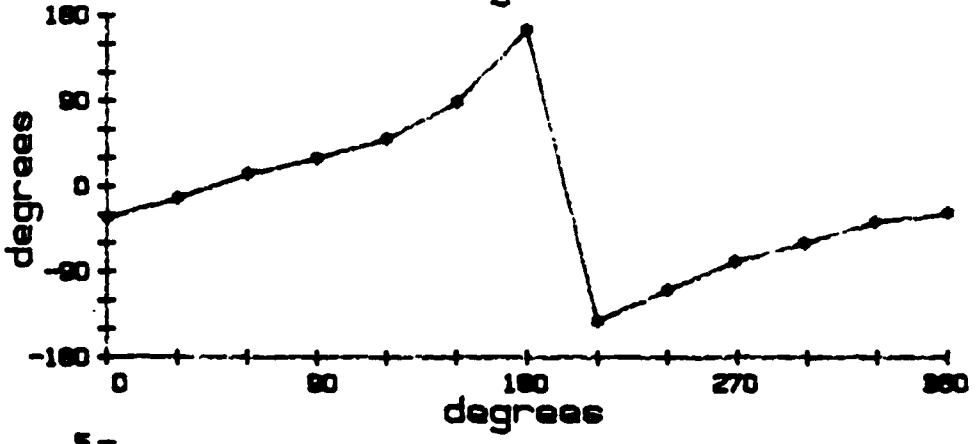
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PQ DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOQ ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

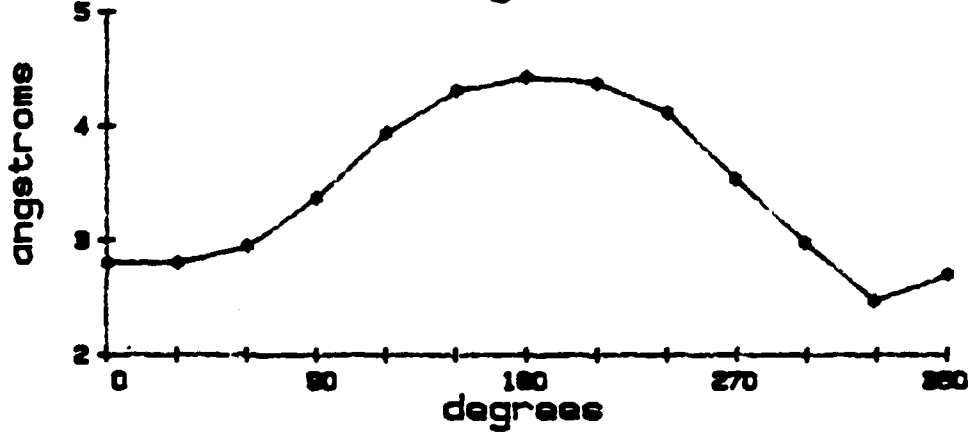
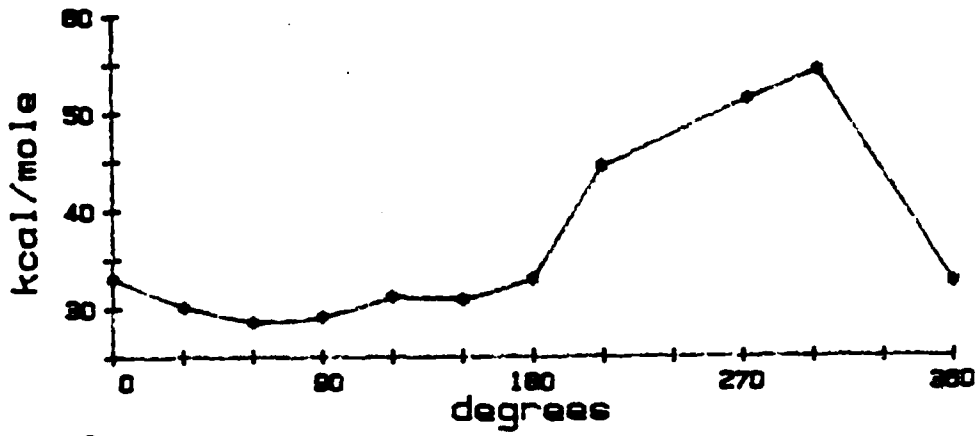


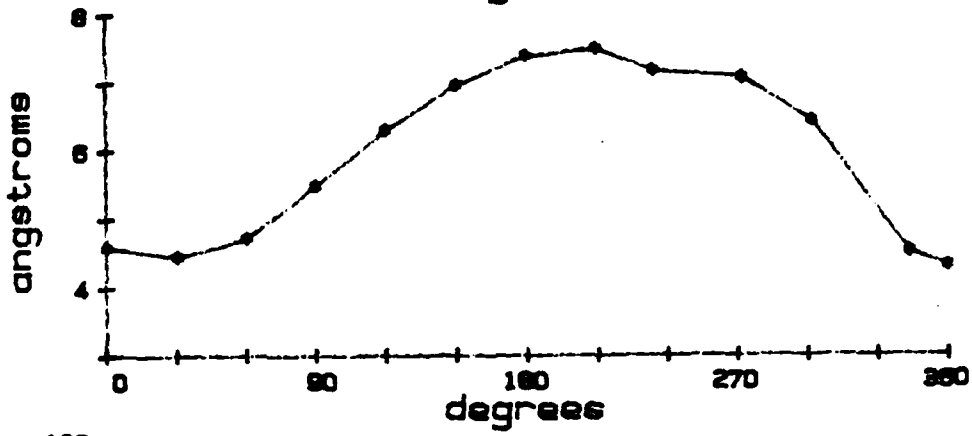
FIGURE 11

ALLOMUSCARINE

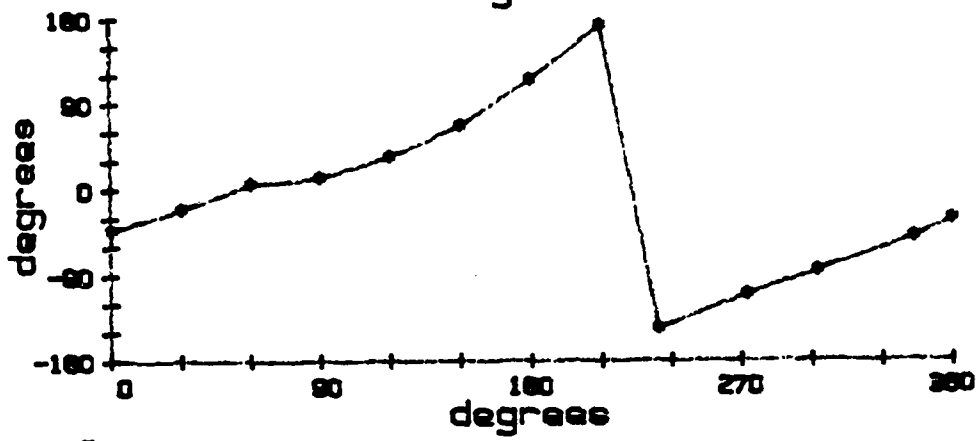
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PQ DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOQ ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

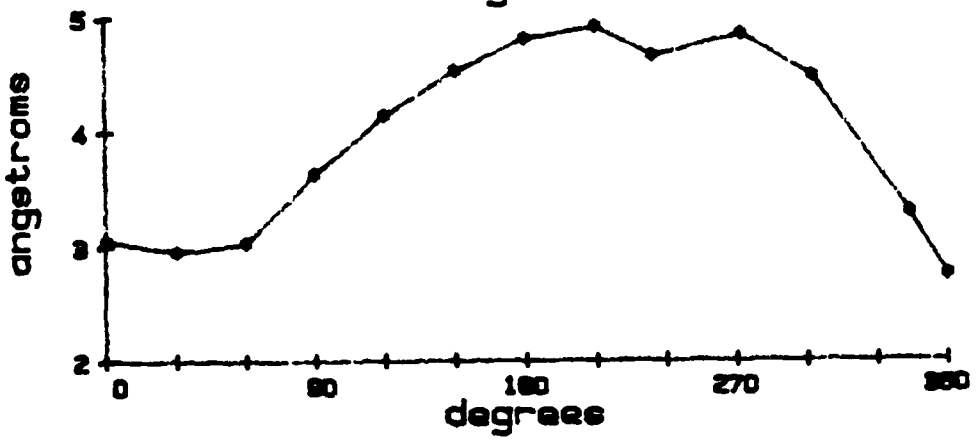
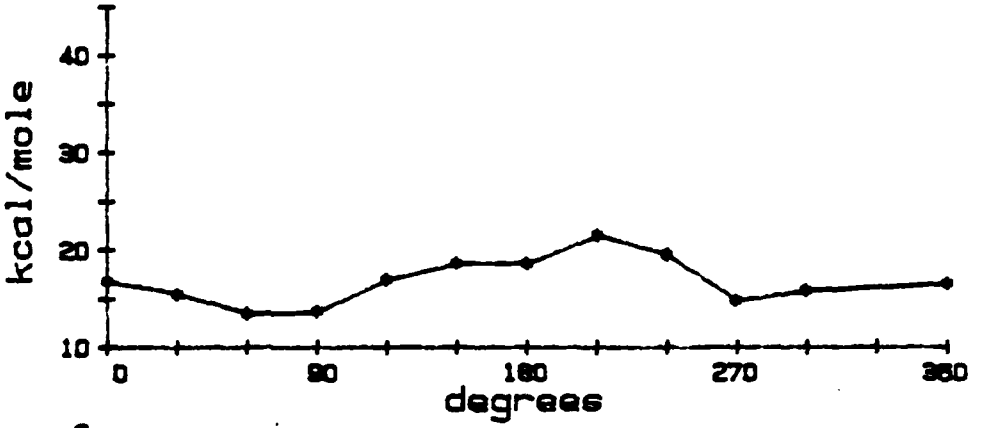


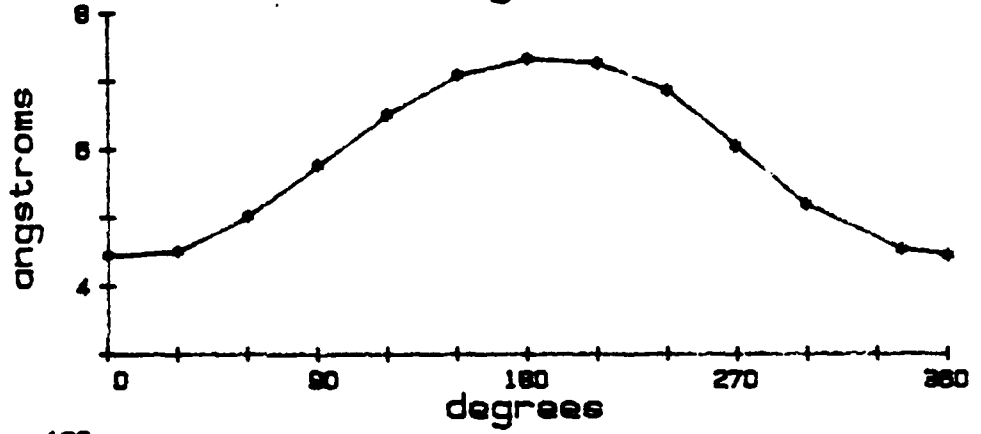
FIGURE 12

DEHYDRO MUSCARINE

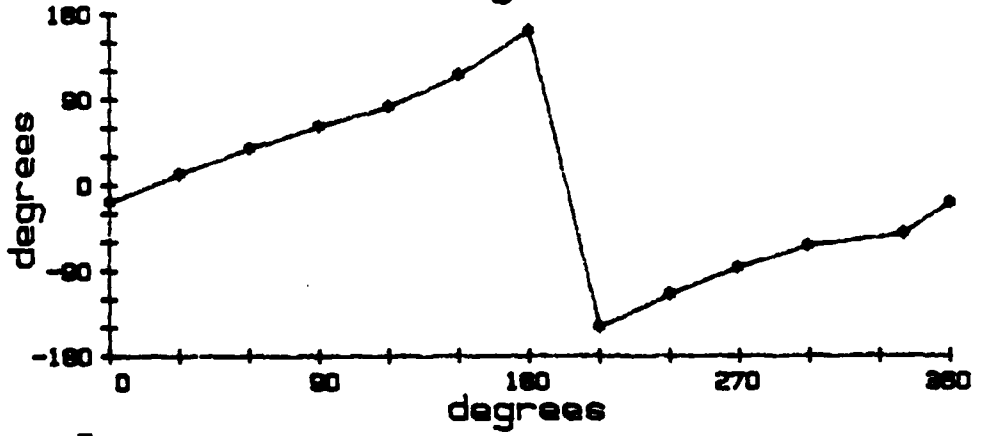
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PQ DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOQ ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

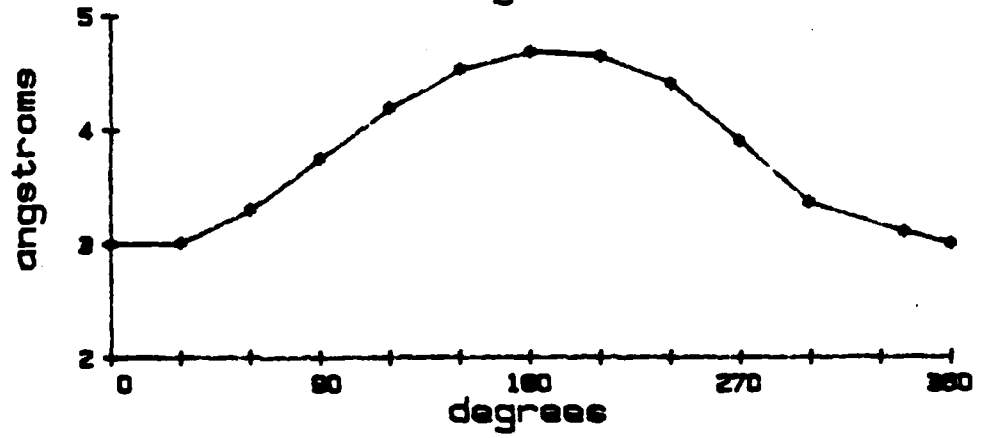
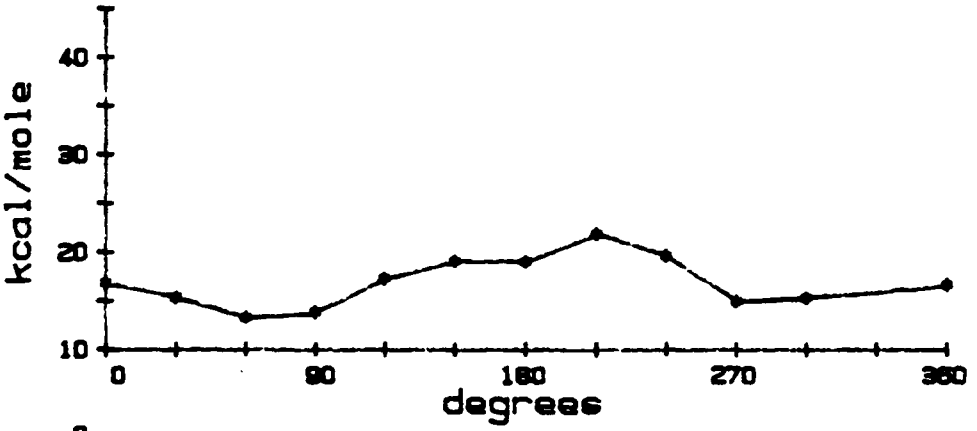


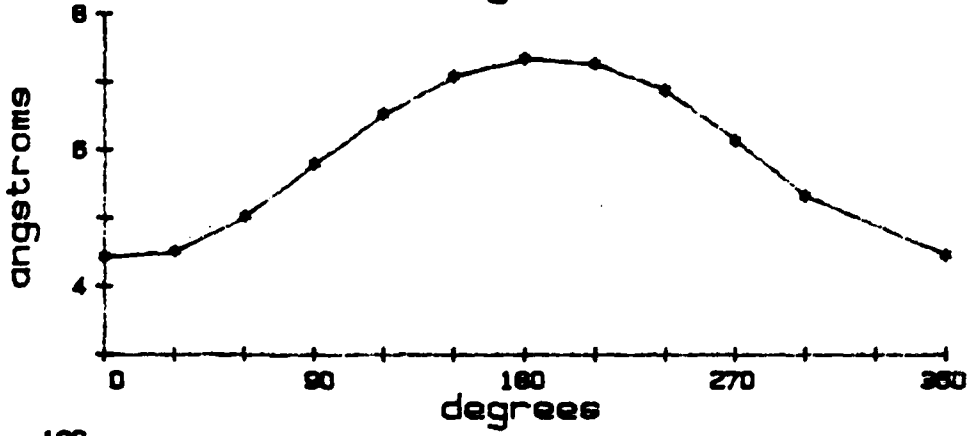
FIGURE 13

DEHYDRO EPIALLOMUSCARINE

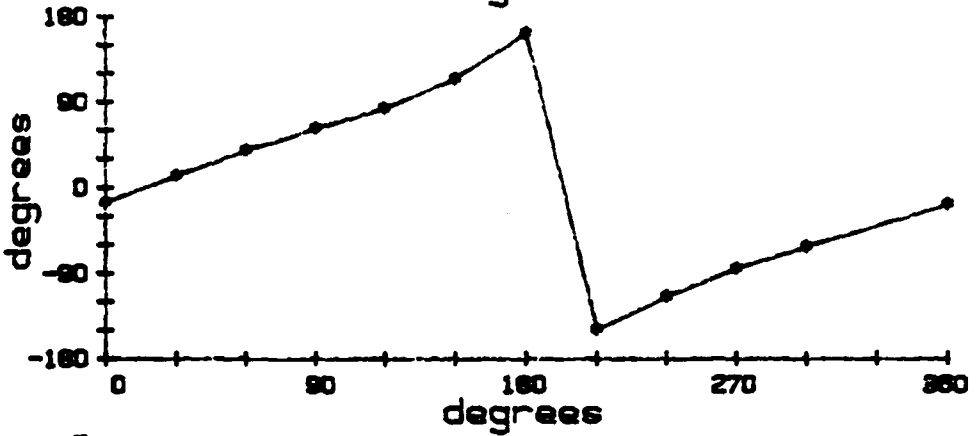
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PQ DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOQ ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

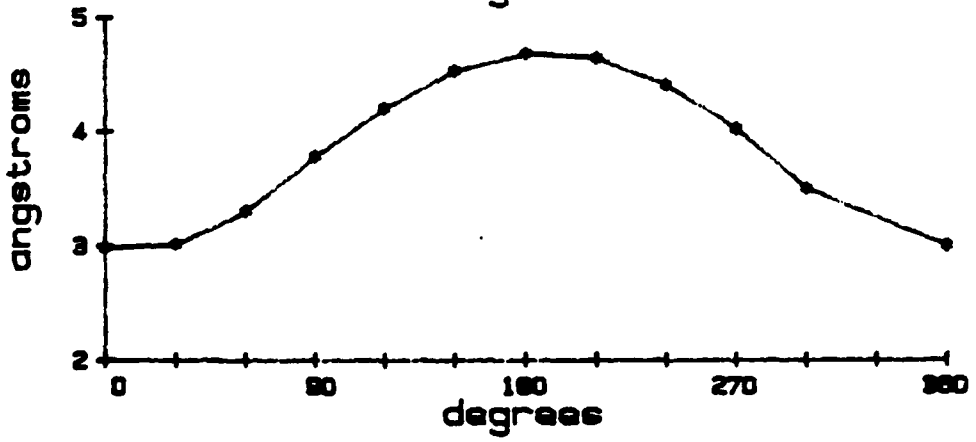
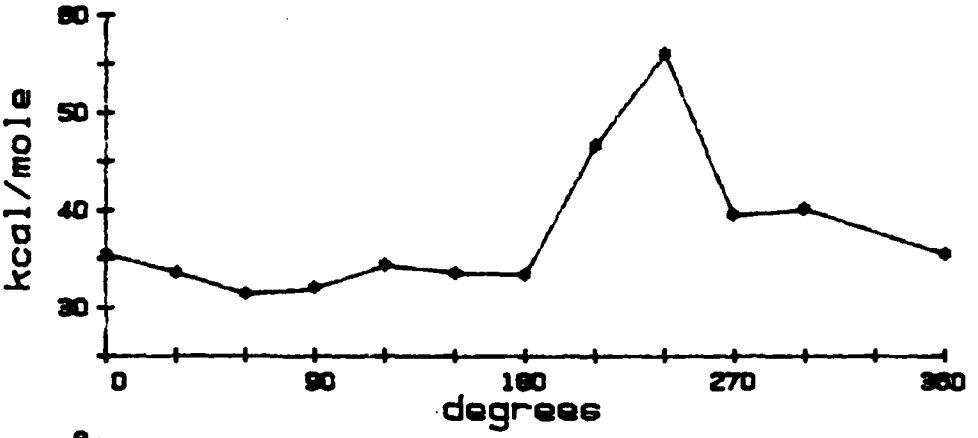


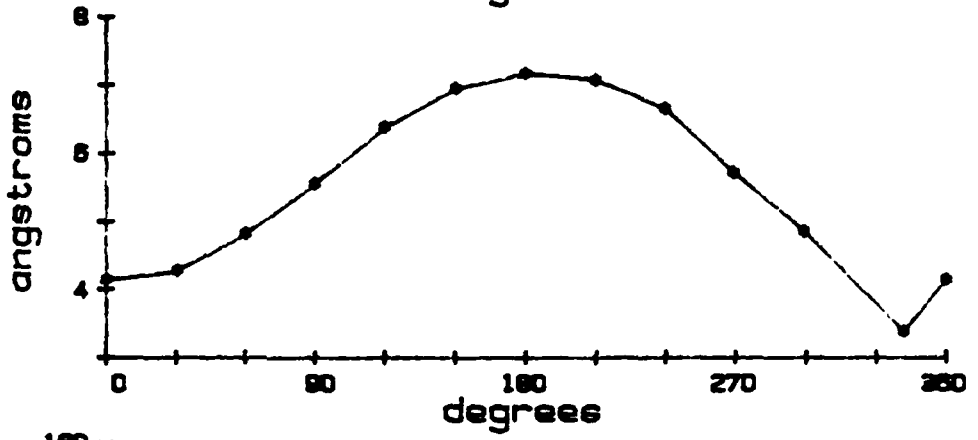
FIGURE 14

cis MUSCARONE

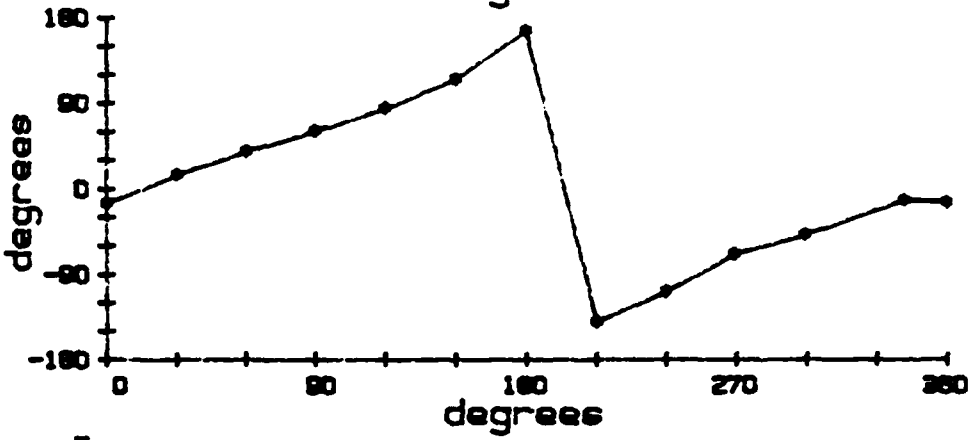
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PQ DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOQ ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

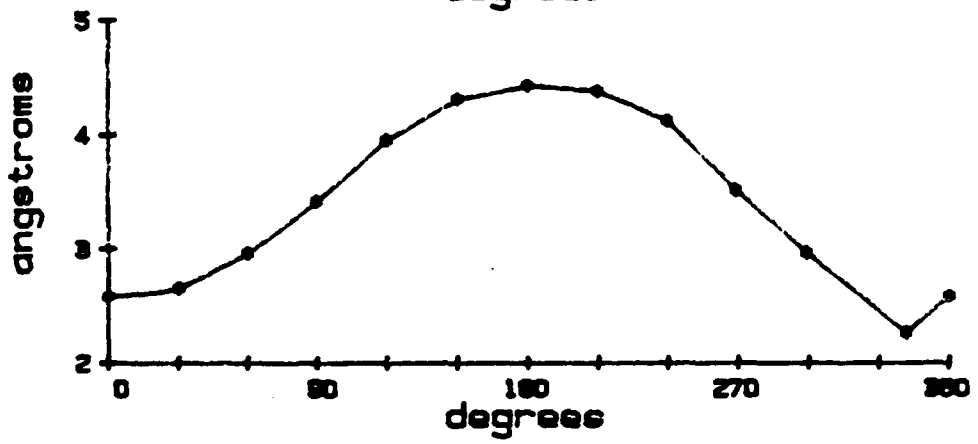
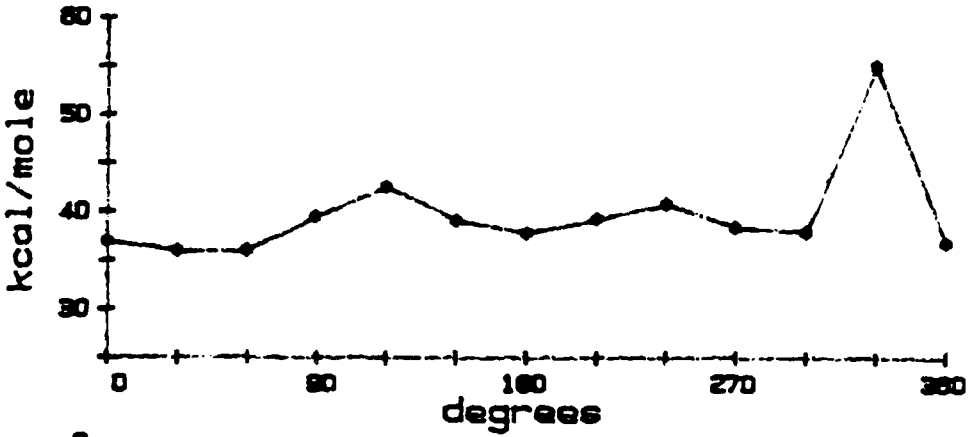


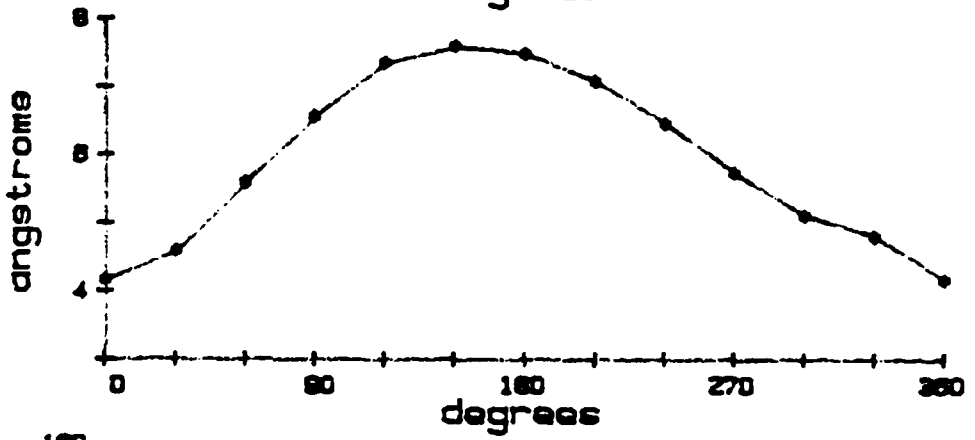
FIGURE 15

trans MUSCARONE

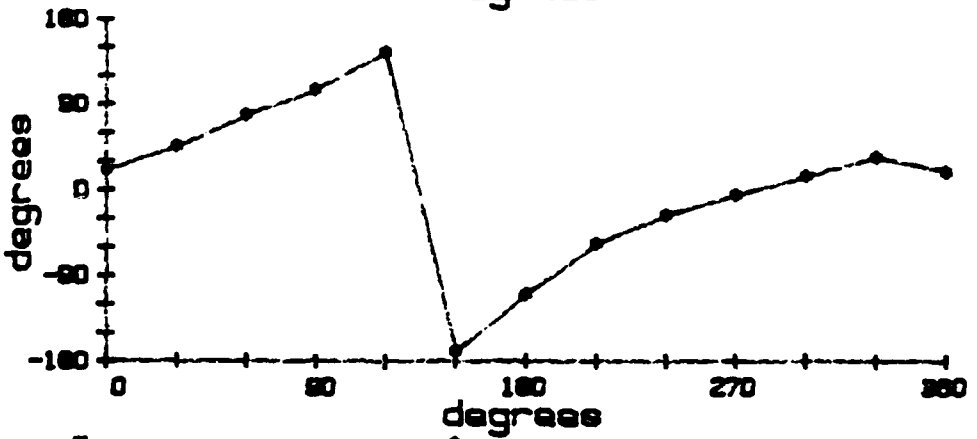
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PQ DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOQ ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

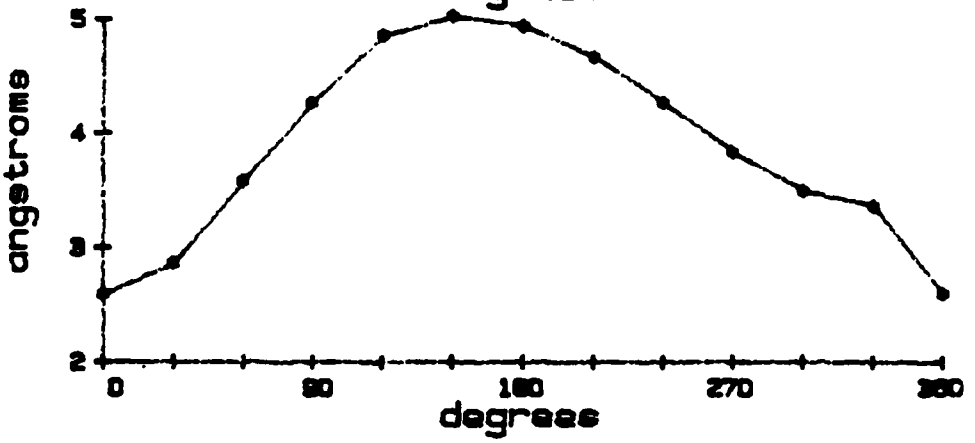
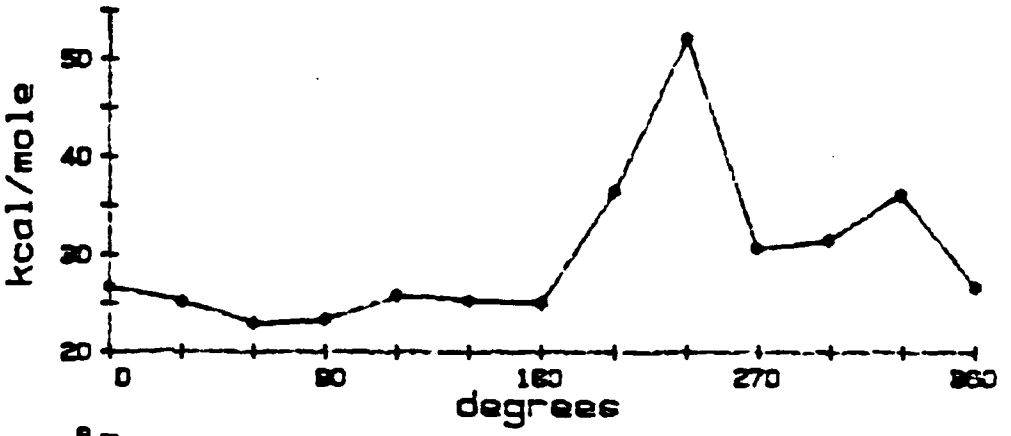


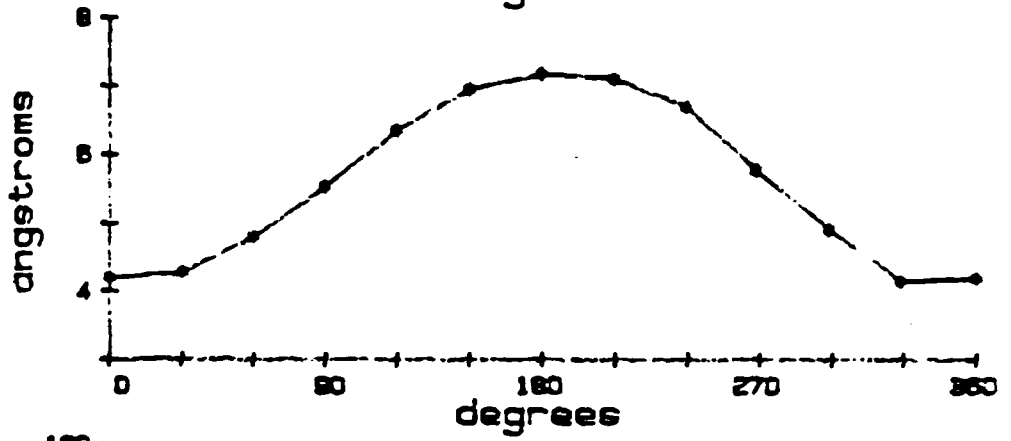
FIGURE 16

cis F-2268

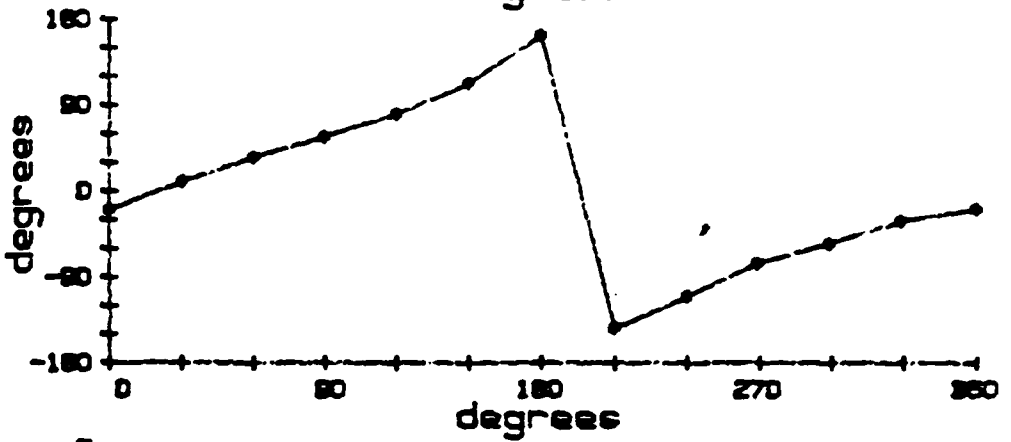
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PO DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOO ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

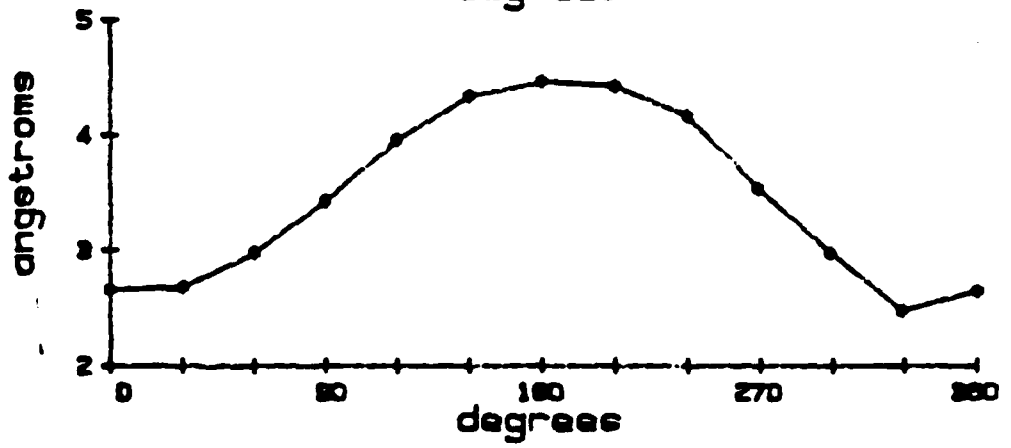
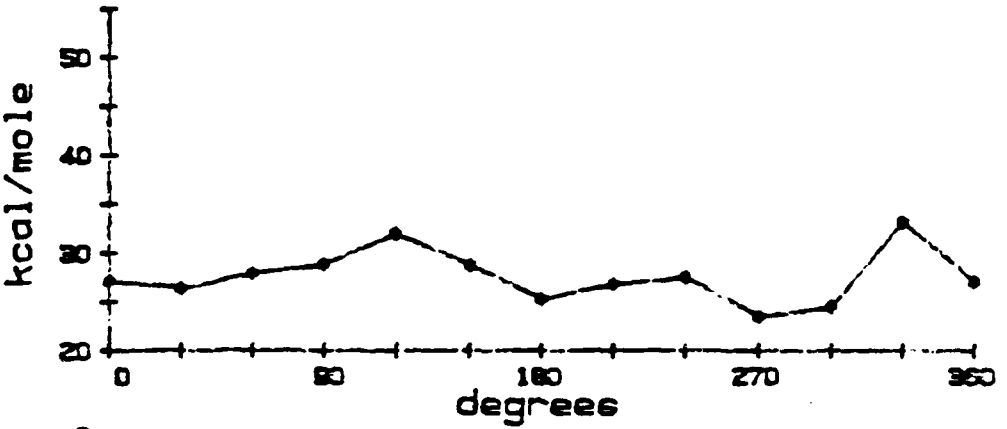


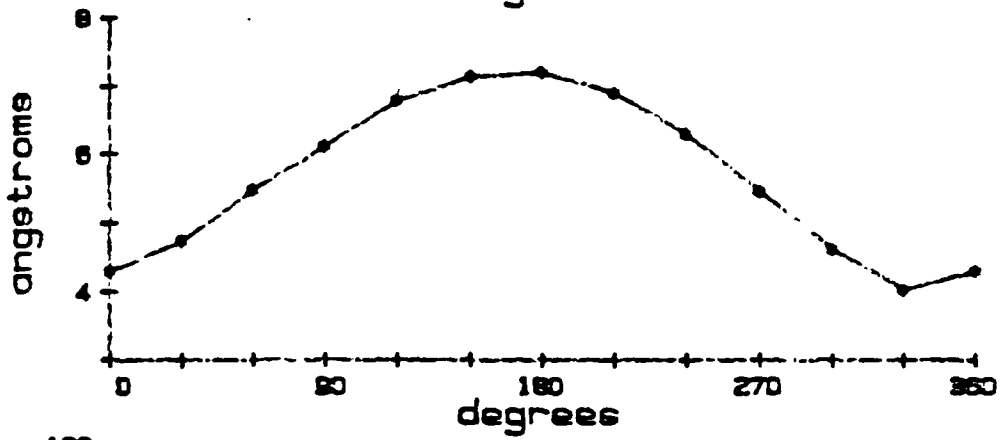
FIGURE 17

trans F-2268

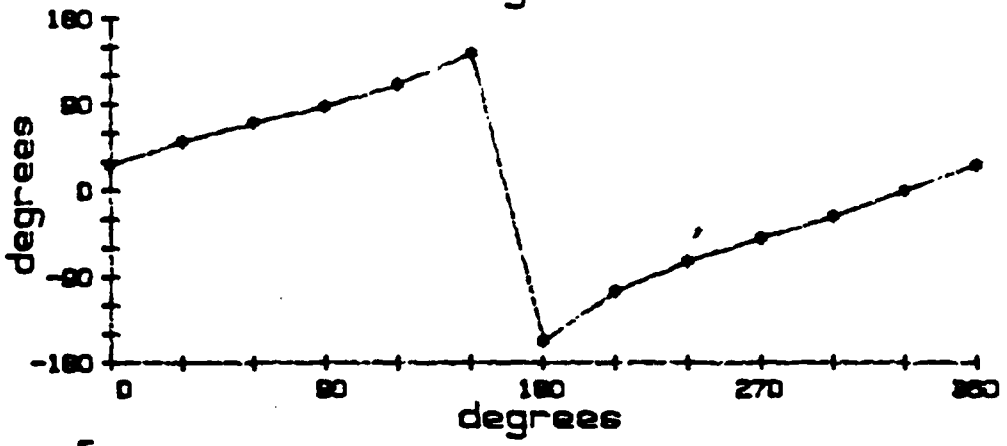
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PO DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOO ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

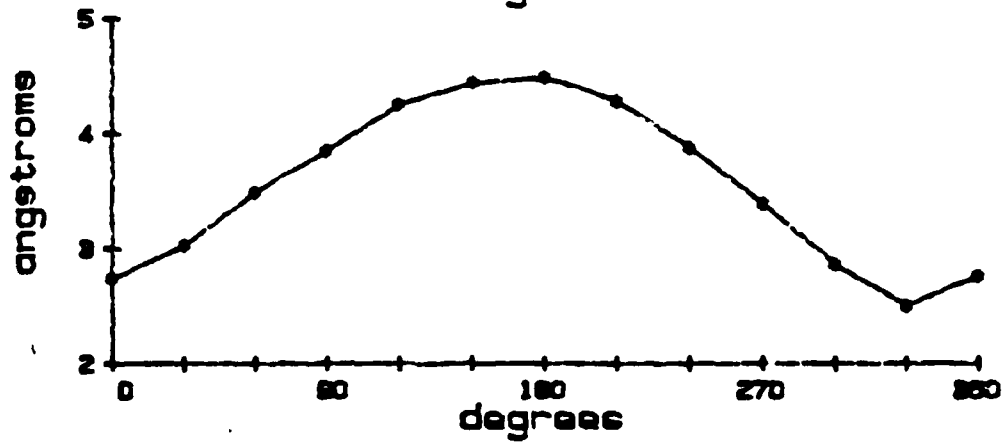
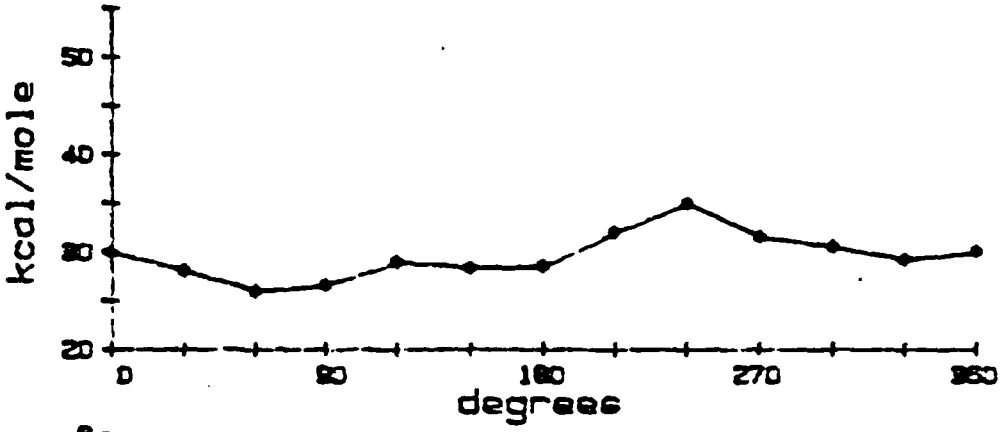


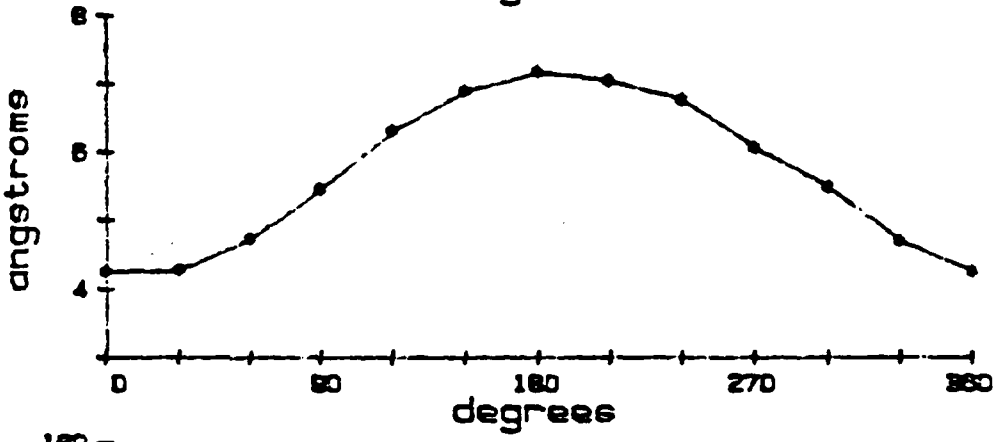
FIGURE 18

TFTM

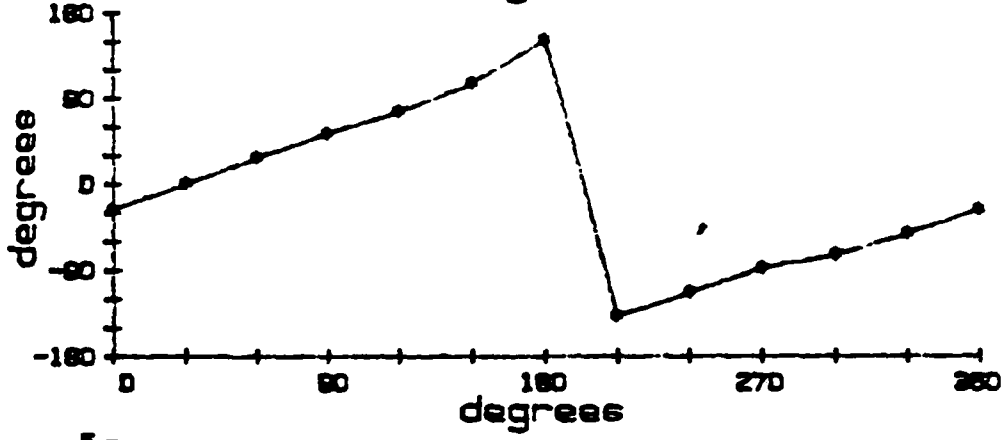
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PO DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOO ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

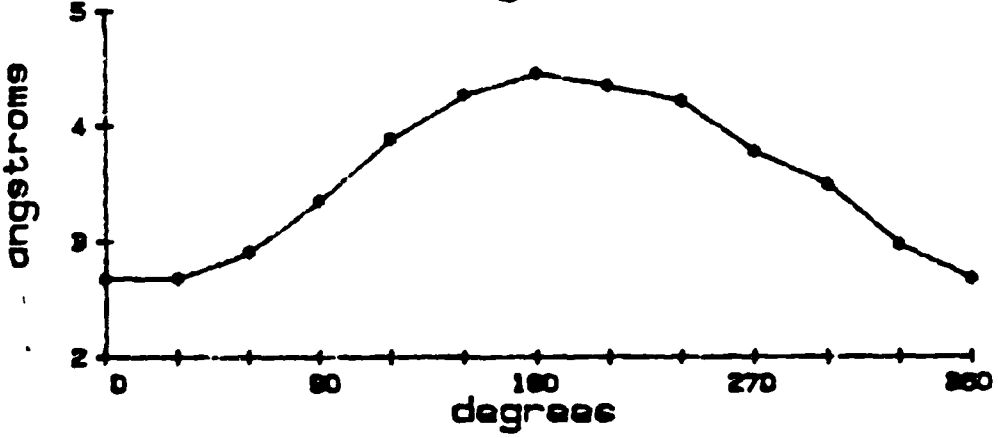
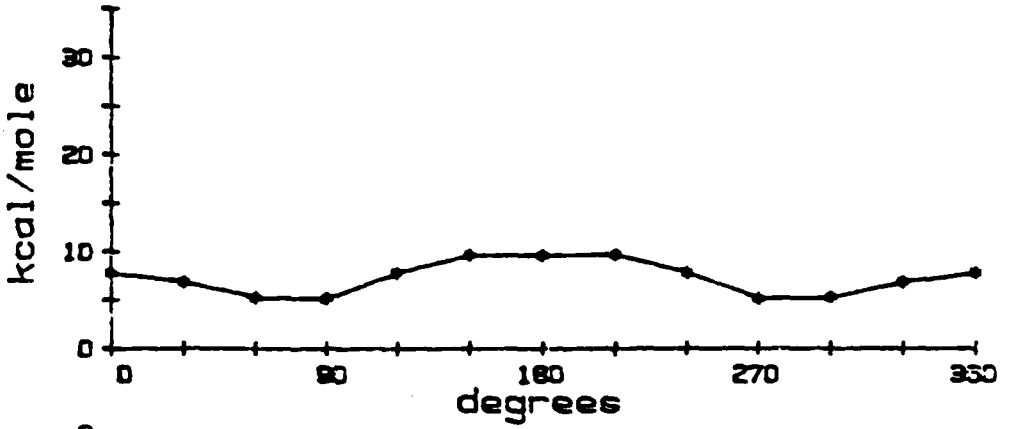


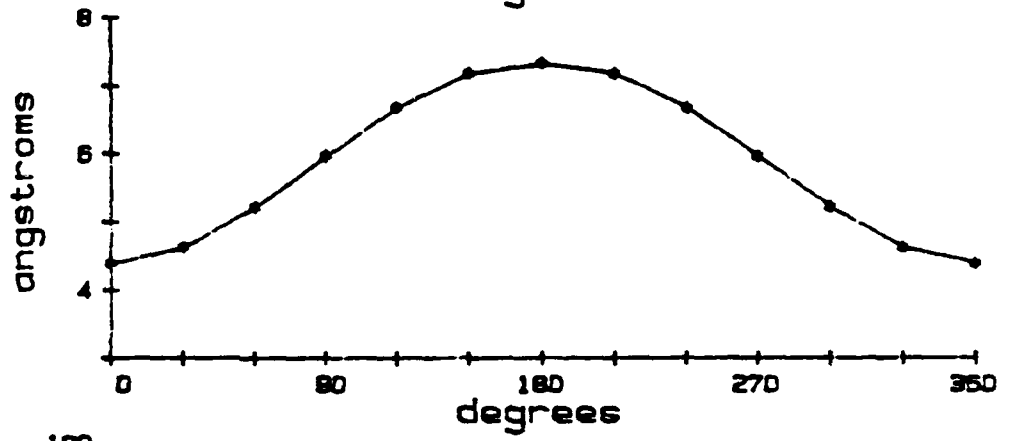
FIGURE 19

5-METHYLFURMETHIDE

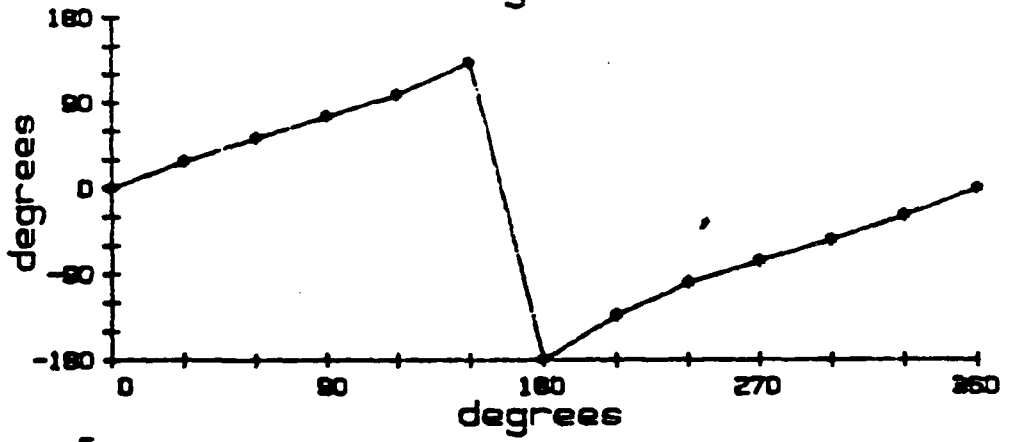
CONFORMATIONAL ENERGY vs. NCCO TORSION ANGLE



SCHULMAN PQ DISTANCE vs. NCCO TORSION ANGLE



SCHULMAN PNOQ ANGLE vs. NCCO TORSION ANGLE



BEERS DISTANCE vs. NCCO TORSION ANGLE

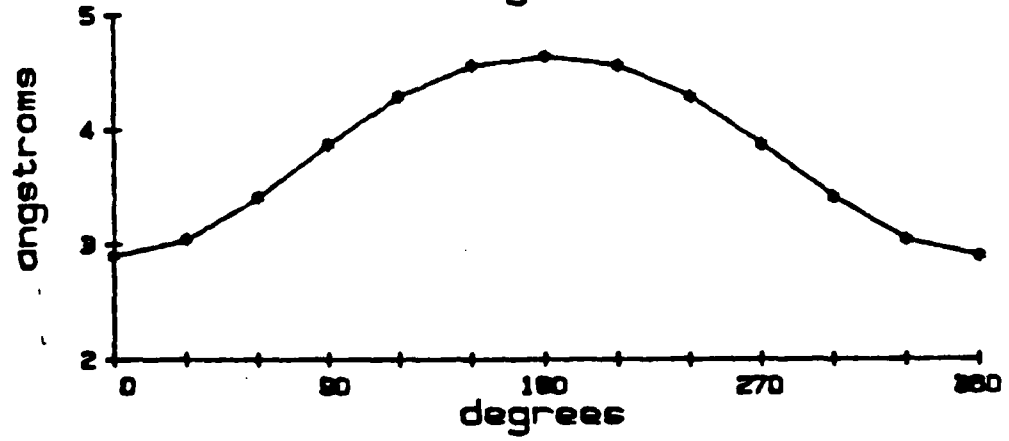
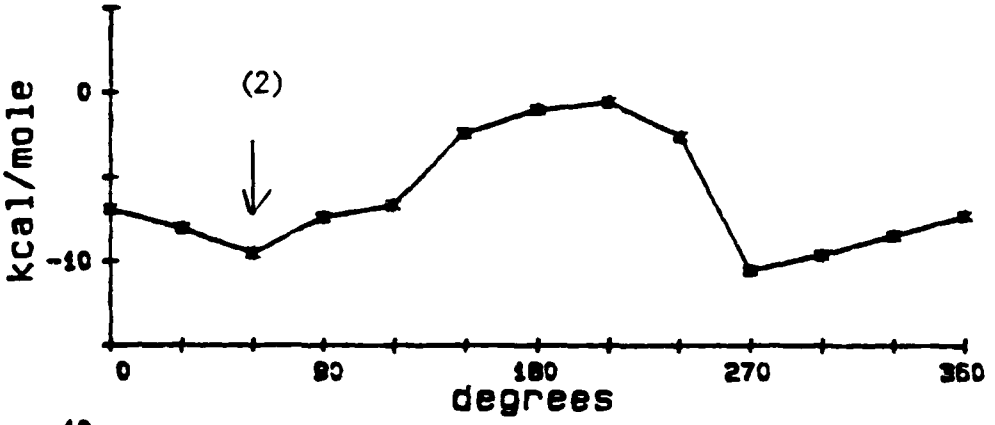


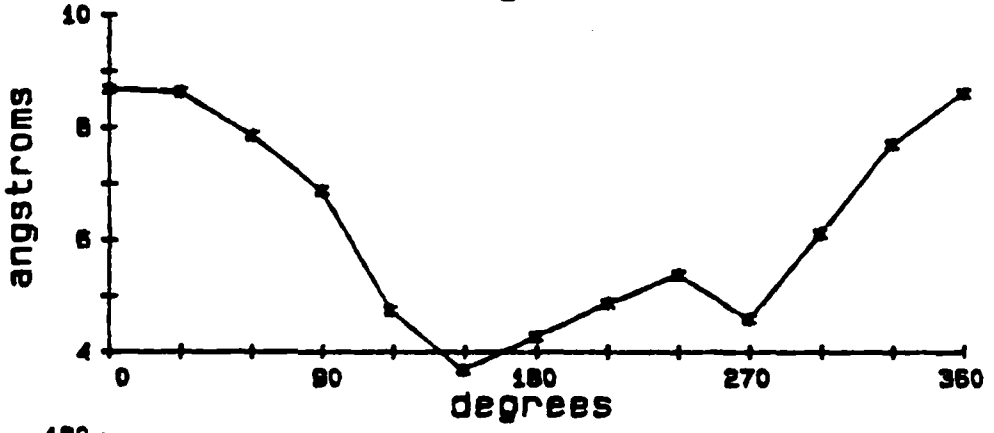
FIGURE 41

PILOCARPINE #2

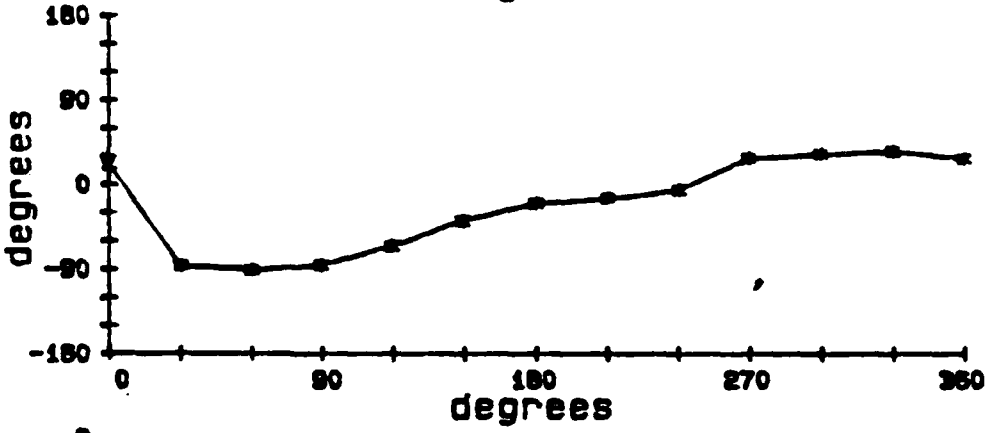
CONFORMATIONAL ENERGY VS. TAO 1



SCHULMAN PQ DISTANCE VS. TAO 1



SCHULMAN PNOQ ANGLE VS. TAO 1



BEERS DISTANCE VS. TAO 1

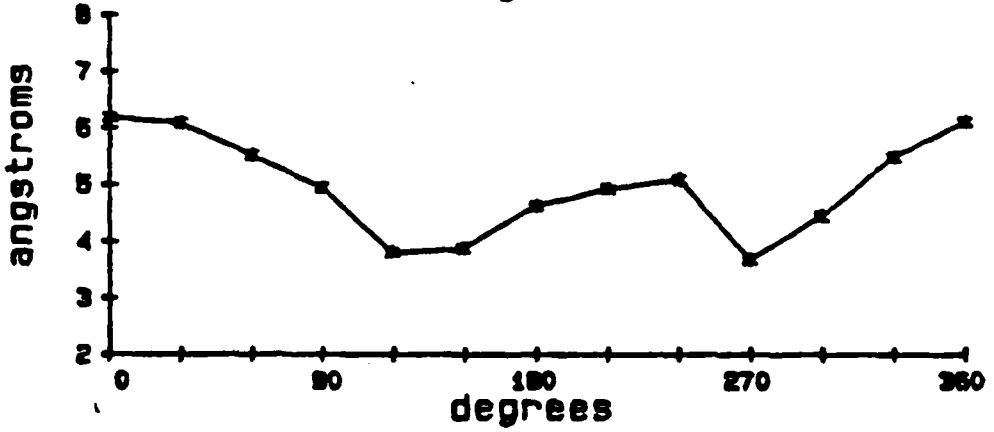
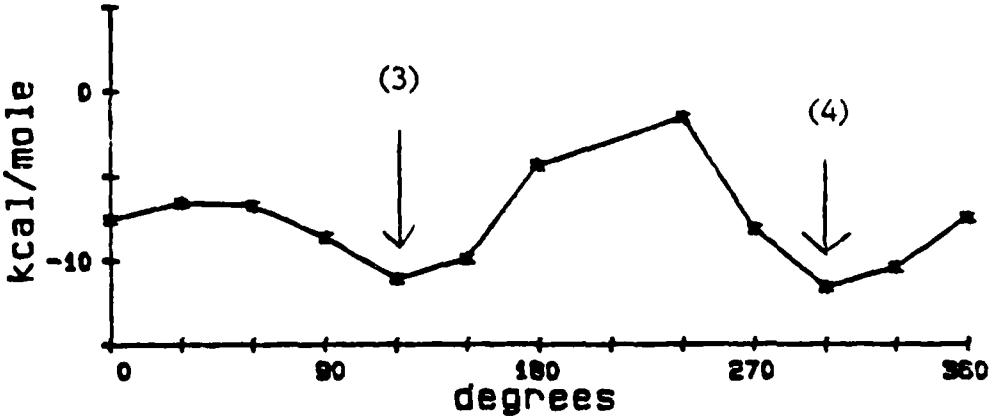


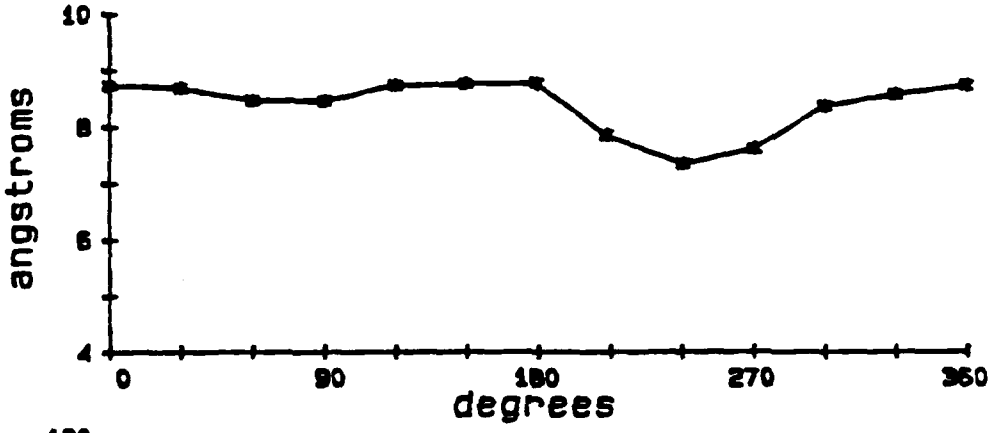
FIGURE 25

PILOCARPINE #3

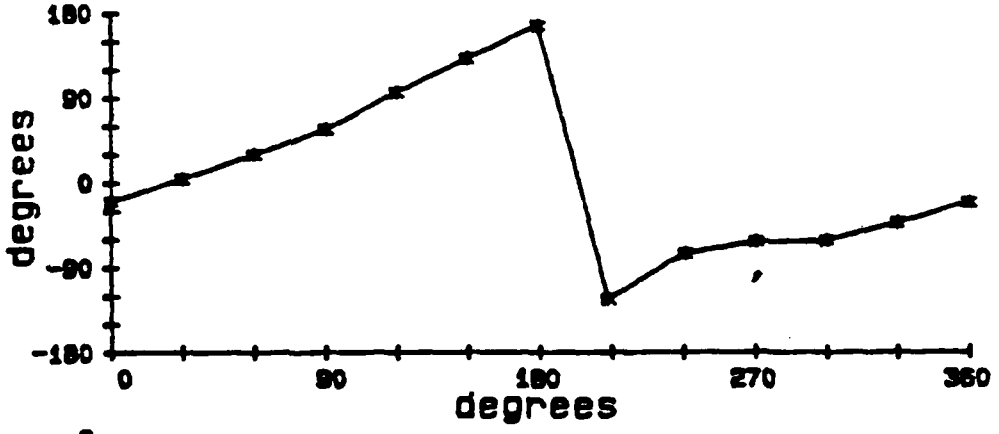
CONFORMATIONAL ENERGY VS. TAD 1



SCHULMAN PQ DISTANCE VS. TAD 1



SCHULMAN PNOQ ANGLE VS. TAD 1



BEERS DISTANCE VS. TAD 1

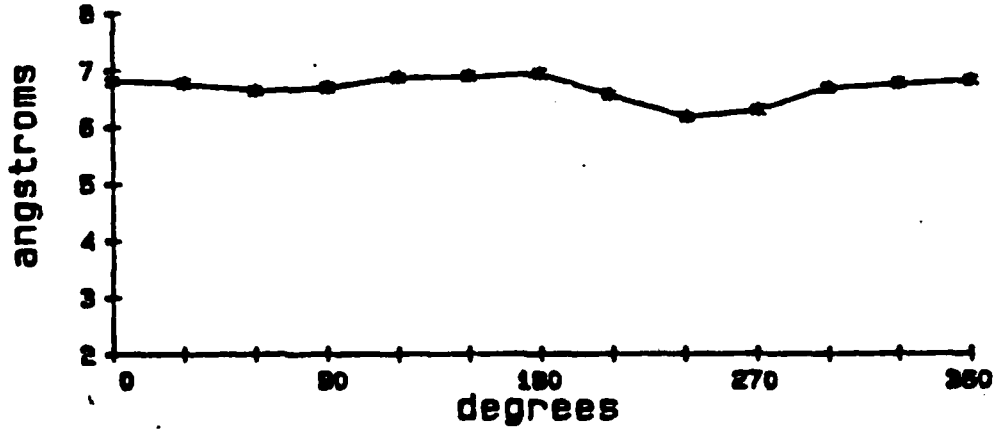


TABLE XXVI

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

MUSCARINE(GLOBAL MINIMUM)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
					0.917
1	O	-0.2528	-0.3299	-0.3314	
2	C	0.1021	0.0747	0.0777	
3	C	0.1520	0.1126	0.0929	
4	C	-0.0170	-0.0347	-0.0321	
5	C	0.1561	0.1061	0.0921	
6	C	-0.0328	0.0269	0.0207	
7	O	-0.2647	-0.3162	-0.3191	
8	C	0.0599	0.0928	0.0679	
9	N	0.0952	-0.1505	-0.0836	
10	C	0.0530	0.1064	0.0813	
11	C	0.0541	0.1051	0.0828	
12	C	0.0544	0.1241	0.0862	
13	H	-0.0039	0.0403	0.0461	
14	H	-0.0083	0.0378	0.0491	
15	H	0.0177	0.0290	0.0353	
16	H	0.0283	0.0554	0.0603	
17	H	-0.0096	0.0346	0.0393	
18	H	0.0260	0.0151	0.0179	
19	H	0.0176	0.0184	0.0209	
20	H	0.0141	0.0072	0.0053	
21	H	0.1580	0.2067	0.1957	
22	H	0.0324	0.0519	0.0608	
23	H	0.0406	0.0667	0.0717	
24	H	0.0548	0.0544	0.0593	
25	H	0.0520	0.0552	0.0594	
26	H	0.0514	0.0619	0.0665	
27	H	0.0527	0.0565	0.0615	
28	H	0.0509	0.0545	0.0592	
29	H	0.0518	0.0586	0.0623	
30	H	0.0612	0.0618	0.0671	
31	H	0.0476	0.0686	0.0771	
32	H	0.0552	0.0481	0.0508	

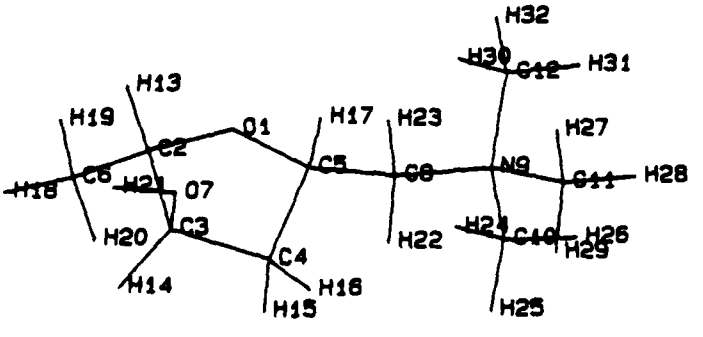


TABLE XXVII

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

+EPIALLOMUSCARINE(LOCAL MINIMUM 162 DEG.)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2273	-0.3131	-0.2963	
2	C	0.1605	0.0910	0.0796	0.903
3	C	0.1525	0.1112	0.0950	
4	C	-0.0259	-0.0433	-0.0454	
5	C	0.1520	0.1201	0.0996	
6	C	-0.0321	0.0372	0.0264	
7	O	-0.2623	-0.3080	-0.3150	
8	C	0.0583	0.0726	0.0487	
9	N	0.0964	-0.1509	-0.0837	
10	C	0.0518	0.1092	0.0805	
11	C	0.0546	0.1088	0.0832	
12	C	0.0528	0.1123	0.0809	
13	H	-0.0203	0.0168	0.0227	
14	H	-0.0072	0.0314	0.0486	
15	H	0.0086	0.0215	0.0260	
16	H	0.0137	0.0502	0.0481	
17	H	-0.0071	0.0298	0.0429	
18	H	0.0226	0.0087	0.0104	
19	H	0.0232	0.0232	0.0197	
20	H	0.0220	0.0180	0.0257	
21	H	0.1588	0.2033	0.1971	
22	H	0.0349	0.0537	0.0645	
23	H	0.0383	0.0746	0.0777	
24	H	0.0537	0.0560	0.0618	
25	H	0.0518	0.0561	0.0600	
26	H	0.0530	0.0586	0.0621	
27	H	0.0514	0.0566	0.0611	
28	H	0.0538	0.0566	0.0619	
29	H	0.0549	0.0602	0.0649	
30	H	0.0561	0.0634	0.0666	
31	H	0.0547	0.0611	0.0660	
32	H	0.0518	0.0533	0.0587	

+same numbering scheme as muscarine

TABLE XXVIII

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

+EPIMUSCARINE(LOCAL MINIMUM 151 DEG.)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2273	-0.3060	-0.2936	
2	C	0.1602	0.0872	0.0796	0.915
3	C	0.1504	0.1075	0.0967	
4	C	-0.0260	-0.0482	-0.0460	
5	C	0.1537	0.1174	0.1068	
6	C	-0.0324	0.0387	0.0291	
7	O	-0.2700	-0.3170	-0.3258	
8	C	0.0603	0.0848	0.0460	
9	N	0.0957	-0.1517	-0.0858	
10	C	0.0531	0.1082	0.0921	
11	C	0.0544	0.1104	0.0940	
12	C	0.0530	0.1062	0.0920	
13	H	-0.0140	0.0225	0.0308	
14	H	-0.0054	0.0362	0.0519	
15	H	0.0044	0.0358	0.0350	
16	H	0.0216	0.0341	0.0453	
17	H	-0.0174	0.0178	0.0253	
18	H	0.0231	0.0097	0.0119	
19	H	0.0230	0.0207	0.0274	
20	H	0.0198	0.0187	0.0147	
21	H	0.1591	0.2062	0.1981	
22	H	0.0418	0.0690	0.0828	
23	H	0.0400	0.0752	0.0783	
24	H	0.0544	0.0585	0.0640	
25	H	0.0514	0.0549	0.0587	
26	H	0.0514	0.0553	0.0583	
27	H	0.0511	0.0557	0.0591	
28	H	0.0540	0.0584	0.0636	
29	H	0.0547	0.0599	0.0644	
30	H	0.0559	0.0618	0.0661	
31	H	0.0547	0.0599	0.0624	
32	H	0.0513	0.0581	0.0573	

+ same numbering scheme as muscarine

TABLE XXIX

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

+ALLOMUSCARINE(LOCAL MINIMUM 131 DEG.)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2313	-0.3127	-0.2904	
2	C	0.1504	0.0810	0.0671	0.903
3	C	0.1486	0.1012	0.0869	
4	C	-0.0234	-0.0385	-0.0379	
5	C	0.1539	0.1130	0.0954	
6	C	-0.0312	0.0300	0.0262	
7	O	-0.2748	-0.3223	-0.3338	
8	C	0.0561	0.0733	0.0324	
9	N	0.0963	-0.1536	-0.0843	
10	C	0.0525	0.1076	0.0821	
11	C	0.0541	0.1111	0.0839	
12	C	0.0526	0.1125	0.0823	
13	H	-0.0124	0.0345	0.0328	
14	H	-0.0063	0.0399	0.0511	
15	H	0.0136	0.0442	0.0425	
16	H	0.0288	0.0431	0.0537	
17	H	-0.0159	0.0328	0.0445	
18	H	0.0233	0.0113	0.0128	
19	H	0.0200	0.0133	0.0138	
20	H	0.0224	0.0231	0.0268	
21	H	0.1597	0.2053	0.1995	
22	H	0.0396	0.0633	0.0813	
23	H	0.0422	0.0692	0.0744	
24	H	0.0534	0.0577	0.0629	
25	H	0.0527	0.0556	0.0600	
26	H	0.0524	0.0559	0.0596	
27	H	0.0513	0.0557	0.0597	
28	H	0.0538	0.0564	0.0633	
29	H	0.0544	0.0598	0.0635	
30	H	0.0557	0.0601	0.0664	
31	H	0.0563	0.0635	0.0650	
32	H	0.0511	0.0531	0.0569	

+same numbering scheme as muscarine

TABLE XXX

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

DEHYDRO-MUSCARINE(GLOBAL MINIMUM) (TRANS)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE (MNDO)
1	O	-0.2299	-0.2665	-0.2438	
2	C	0.1638	0.0802	0.0984	
3	C	0.1551	0.1414	0.1329	1.005
4	C	-0.0601	-0.0965	-0.1304	
5	C	0.1339	-0.0354	-0.0361	
6	C	-0.0374	0.0195	0.0044	
7	O	-0.2612	-0.3099	-0.3049	
8	C	0.0673	0.1744	0.1433	
9	N	0.0985	-0.1548	-0.0870	
10	C	0.0520	0.1099	0.0804	
11	C	0.0529	0.1066	0.0814	
12	C	0.0524	0.1177	0.0810	
13	H	0.0059	0.0596	0.0917	
14	H	-0.0053	0.0427	0.0547	
15	H	0.0184	0.1051	0.0912	
16	H	0.0290	0.0180	0.0243	
17	H	0.0215	0.0232	0.0254	
18	H	0.0112	0.0085	0.0006	
19	H	0.1582	0.2041	0.1934	
20	H	0.0392	0.0564	0.0670	
21	H	0.0431	0.0721	0.0760	
22	H	0.0527	0.0542	0.0598	
23	H	0.0587	0.0674	0.0758	
24	H	0.0524	0.0526	0.0557	
25	H	0.0521	0.0570	0.0628	
26	H	0.0526	0.0550	0.0590	
27	H	0.0538	0.0578	0.0621	
28	H	0.0639	0.0707	0.0846	
29	H	0.0502	0.0482	0.0542	
30	H	0.0551	0.0601	0.0622	

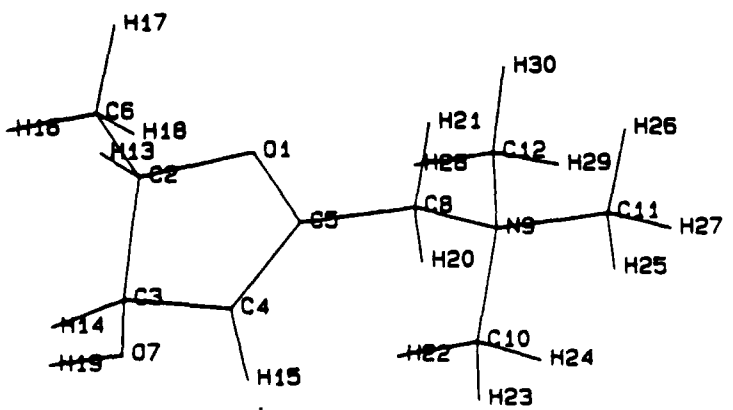


TABLE XXXI

CHARGES FROM MNDO(OPT. & UNOPT.) AND CNDO

+DEHYDRO-MUSCARINE (CIS)-(GLOBAL MINIMUM)

SEQ.	TYPE	CNDO	MNDO(OPT.)	MNDO(UNOPT.)	CATIONIC HEAD CHARGE(MNDO)
1	O	-0.2272	-0.2639	-0.2407	
2	C	0.1665	0.0797	0.0696	1.008
3	C	0.1526	0.1394	0.1311	
4	C	-0.0541	-0.0847	-0.0991	
5	C	0.1311	-0.0399	-0.0425	
6	C	-0.0346	0.0371	0.0290	
7	O	-0.2606	-0.3092	-0.3076	
8	C	0.0673	0.1757	0.1428	
9	N	0.0986	-0.1543	-0.0874	
10	C	0.0514	0.1093	0.0791	
11	C	0.0530	0.1066	0.0819	
12	C	0.0529	0.1168	0.0818	
13	H	-0.0119	0.0364	0.0375	
14	H	-0.0033	0.0404	0.0556	
15	H	0.0181	0.1065	0.0937	
16	H	0.0261	0.0153	0.0153	
17	H	0.0210	0.0157	0.0192	
18	H	0.0204	0.0178	0.0234	
19	H	0.1590	0.2040	0.1963	
20	H	0.0397	0.0572	0.0682	
21	H	0.0427	0.0717	0.0766	
22	H	0.0525	0.0543	0.0597	
23	H	0.0588	0.0662	0.0764	
24	H	0.0530	0.0536	0.0567	
25	H	0.0520	0.0565	0.0626	
26	H	0.0529	0.0550	0.0593	
27	H	0.0540	0.0587	0.0621	
28	H	0.0502	0.0479	0.0543	
29	H	0.0555	0.0609	0.0630	
30	H	0.0623	0.0697	0.0820	

+same numbering scheme as trans dehydro-muscarine

Table XXXII

Muscarinic Agonists

	Compound	[a] Steric Energy	[b] Dihedral Angle	[c] N...O Dist.	[d] Electrostatic Contour
1.	Muscarine	27.71	73.25	3.06	20,40,100,150
		30.06	150	4.3	20,40,100,150
		30.39	180	4.41	30,40,100,150
2.	2 Epimuscarine	31.09	180	4.43	20,40,100,150
		29.52	151	4.32	20,40,100,150
3.	Allomuscarine	31.12	120	4.14	20,40,100,150
		31.30	131.63	4.45	20,40,100,150
		30.79	150	4.53	20,40,100,150
		32.80	180	4.8	20,40,100,150
		28.42	65	3.01	20,40,100,150
4.	Epiallomuscarine	27.90	70	3.05	20,40,100,150
		30.26	150	4.28	20,40,100,150
		30.30	162	4.43	20,40,100,150
		30.58	180	4.48	30,40,100,150
5.	Dehydromuscarine (trans)	16.94	120	4.20	30,40,100,150
		18.64	150	4.53	30,40,100,150
		18.56	180	4.68	30,40,100,150
6.	Dehydromuscarine (cis)	17.25	120	4.21	20,40,100,150
		18.99	180	4.68	30,40,100,150
		19.56	240	4.40	30,40,100,150
		14.94	270	4.01	30,40,100,150
7.	Muscarone (trans)	31.84	287.18	3.1	30,50,70,100 120,160

Table XXXII

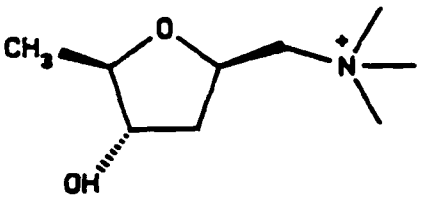
	Compound	[a]Steric Energy	[b]Dihedral Angle	[c]N...O Dist.	[d]Electrostatic Contour
8.	Muscarone	31.14	72.25	3.13	30,50,70,100,120,160
	(cis)	33.47	150.00	4.3	30,50,70,100,120,160
		33.30	180	4.43	30,50,70,100,120,160
9.	F-2268 (cis)		150		30,50,70,100,120,160
		25.03	180	4.47	30,50,70,100,120,160
10.	F-2268 (trans)	22.68	286.62	3.13	30,50,70,100,120,160
		25.30	180	4.48	30,50,70,100,120,160
		26.81	210	4.27	30,50,70,100,120,160
11.	5-Methyl-furmethide	4.94	72.3	3.59	20,30,100,150
		7.8	120	4.29	20,30,100,150
		9.66	150	4.55	20,30,100,150
12.	TFTM	25.74	71.38	3.05	20,30,100,150
		28.32	150.00	4.27	20,30,100,150
		28.50	180.00	4.46	20,30,100,150

a. reported in kilocalories/mole
b. reported in degrees
c. reported in Angstroms (A°)
d. reported in kilocalories

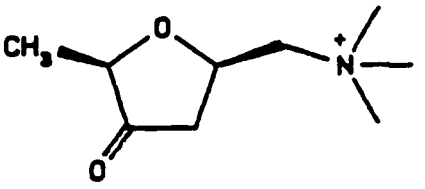
Figure 21 Muscarine (150 dihedral angle) - Electrostatic Potential Contour. Contoured at 150 kcal, 100 kcal, 40 kcal, and 20 kcal. Most positive region is found within the 150 kcal enclosure ($N-CH_3$ groups). Least positive areas are found in the 20 kcal region (oxygens, ring and OH).

Color Coding: yellow, 150 kcal; red, 100 kcal; blue, 40 kcal; light bulue, 20 kcal

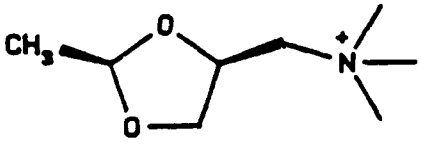
Active Muscarinic Agonists



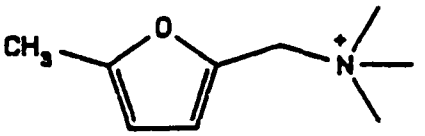
Muscarine



cis-Muscarone

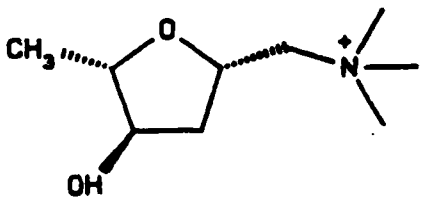


cis-F2268

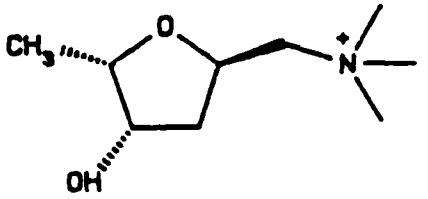


5-Methylfurmethide

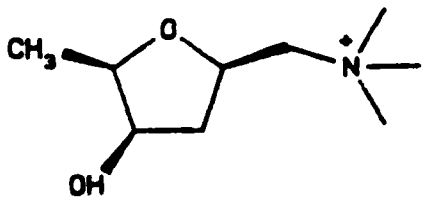
Inactive Muscarinic Agonists



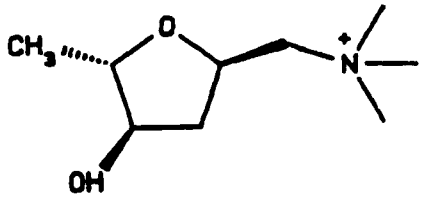
(-) Muscarine



Epiallomuscarine

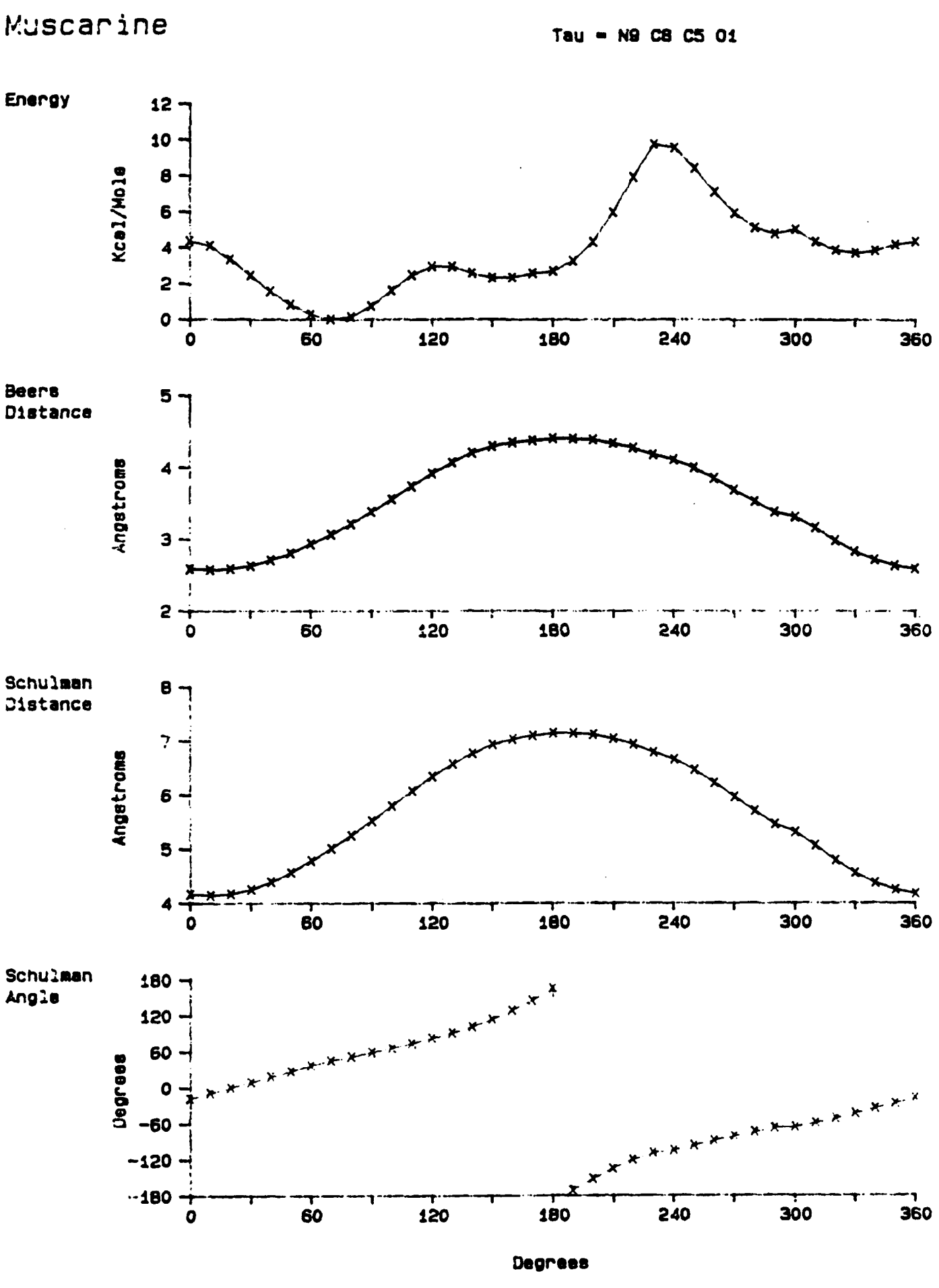


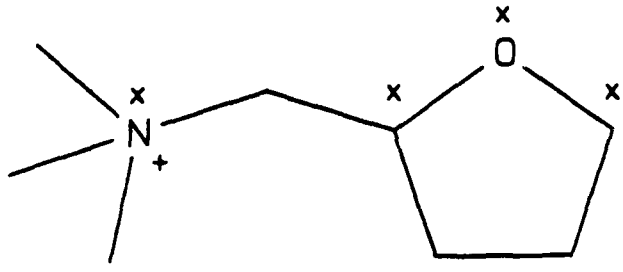
Epimuscarine



Allomuscarine

FIGURE 22

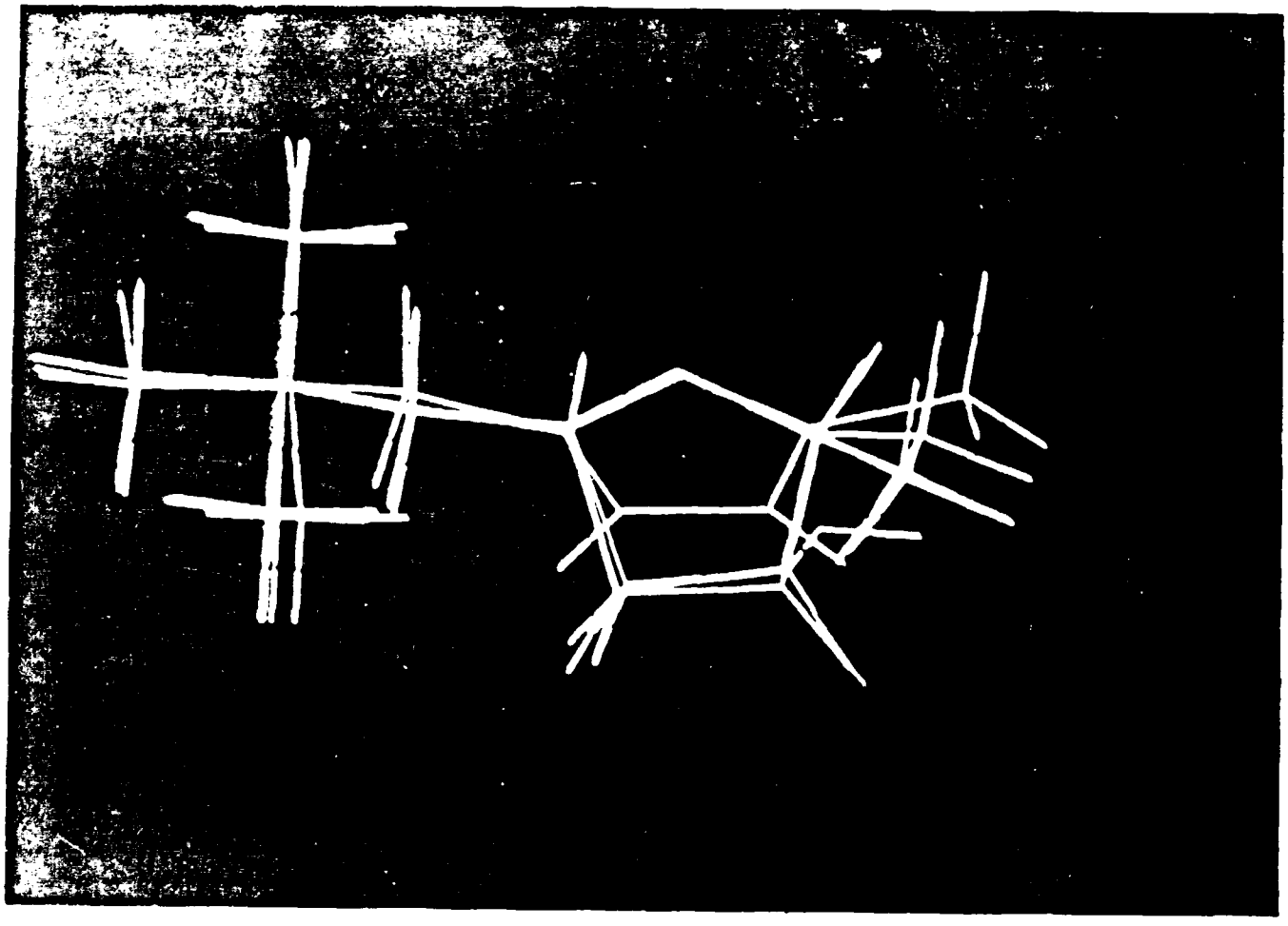

Muscarine
Tau = N9 C8 C5 O1
Energy
Kcal/Mole
12
10
8
6
4
2
0
0
60
120
180
240
300
360
Beers
Distance
Angstroms
5
4
3
2
Schulman
Distance
Angstroms
8
7
6
5
4
Schulman
Angle
Degrees
180
120
60
0
-60
-120
-180
Degrees



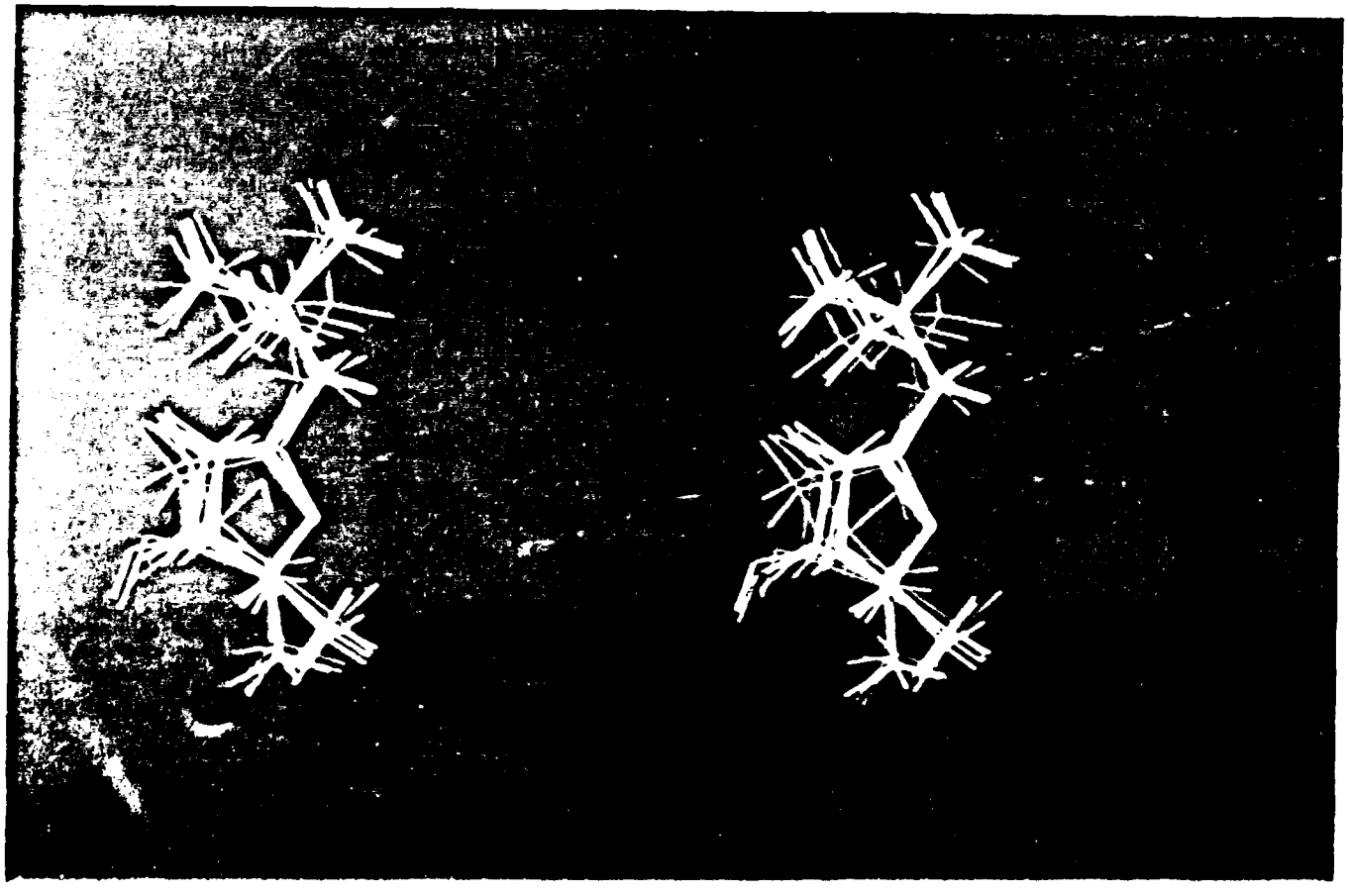
Atoms Fitted for Receptor Mapping

FIGURE 23

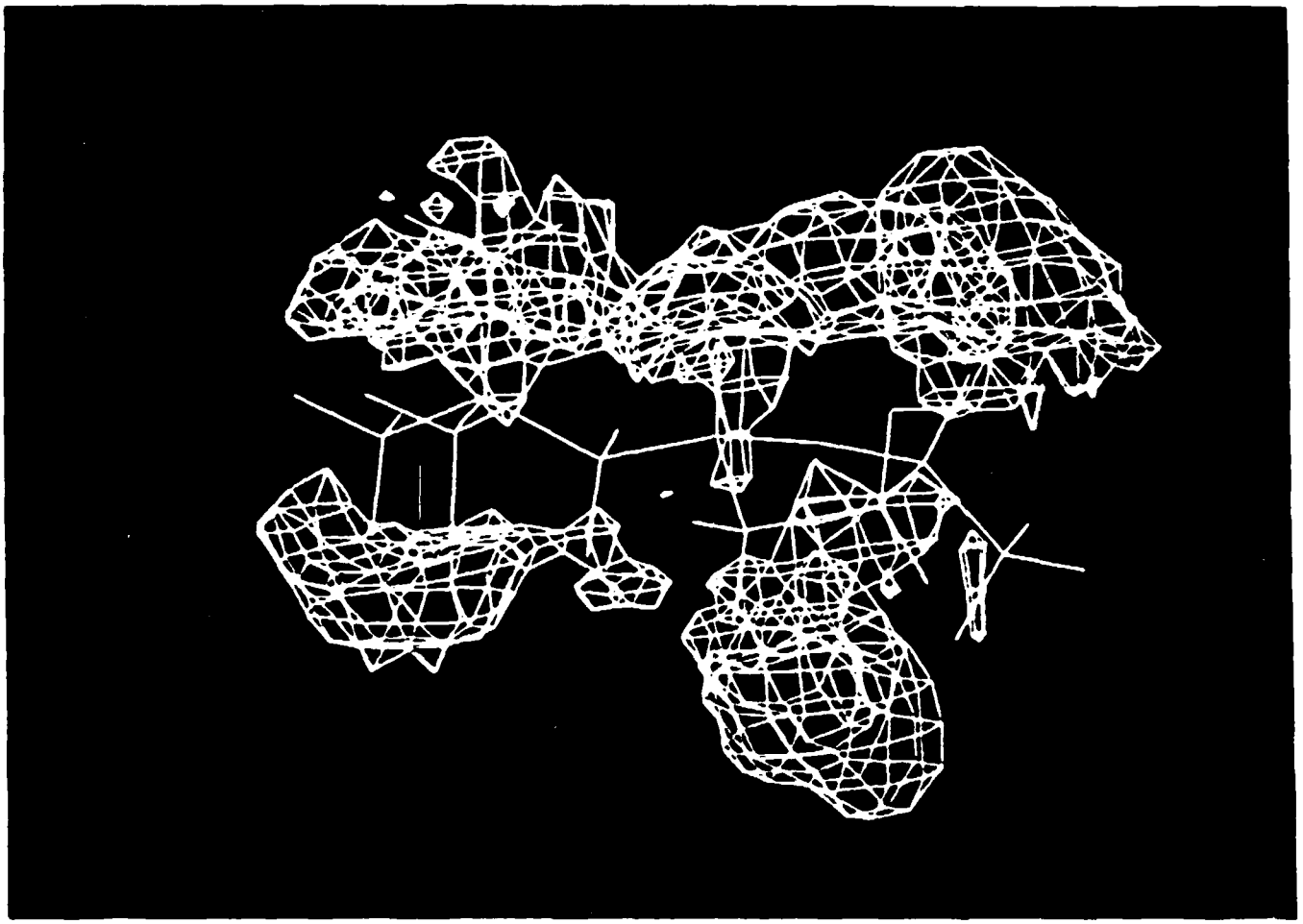
A. Fitting of Active Agonists



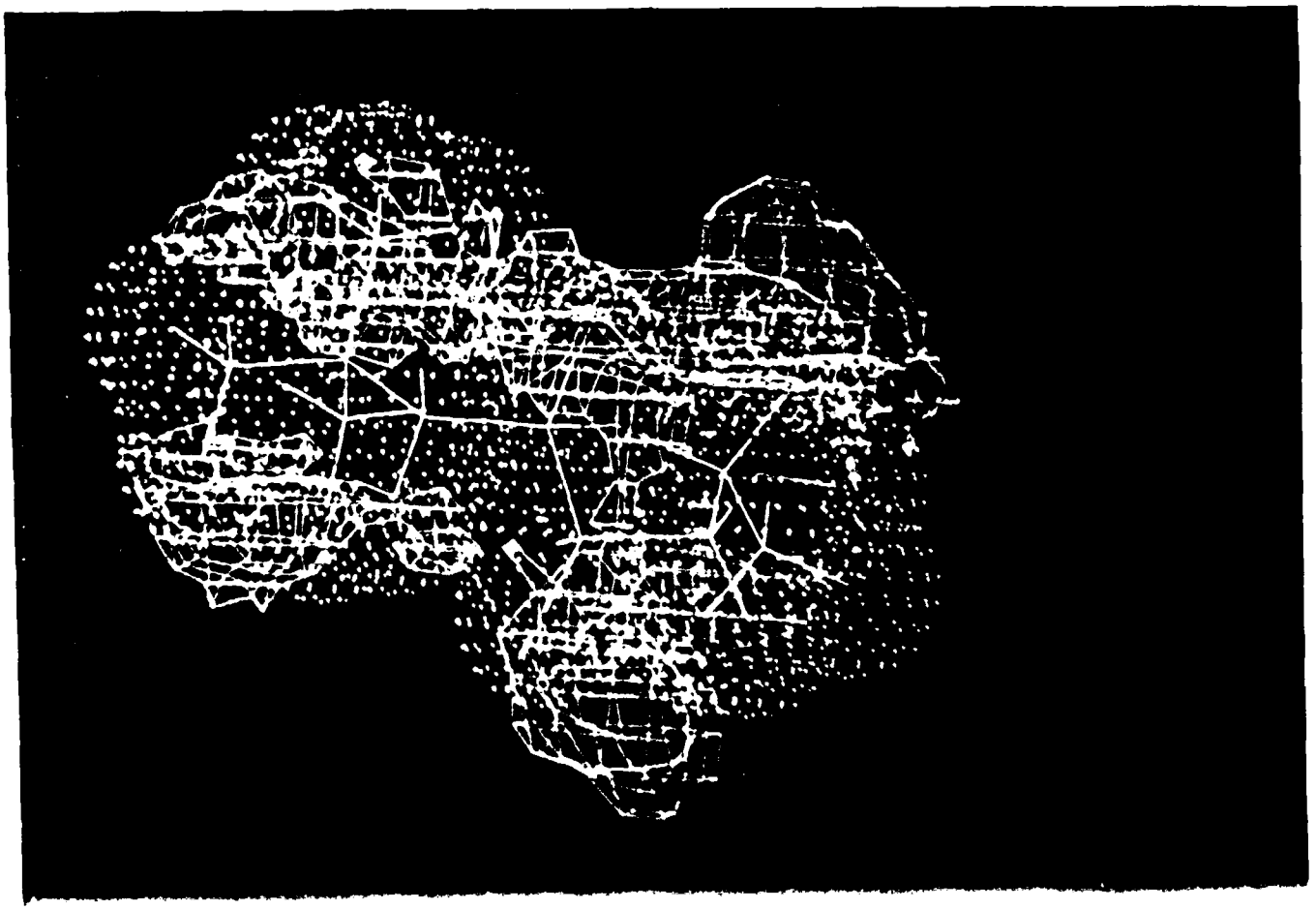
B. Fitting of Active and Inactive Agonists



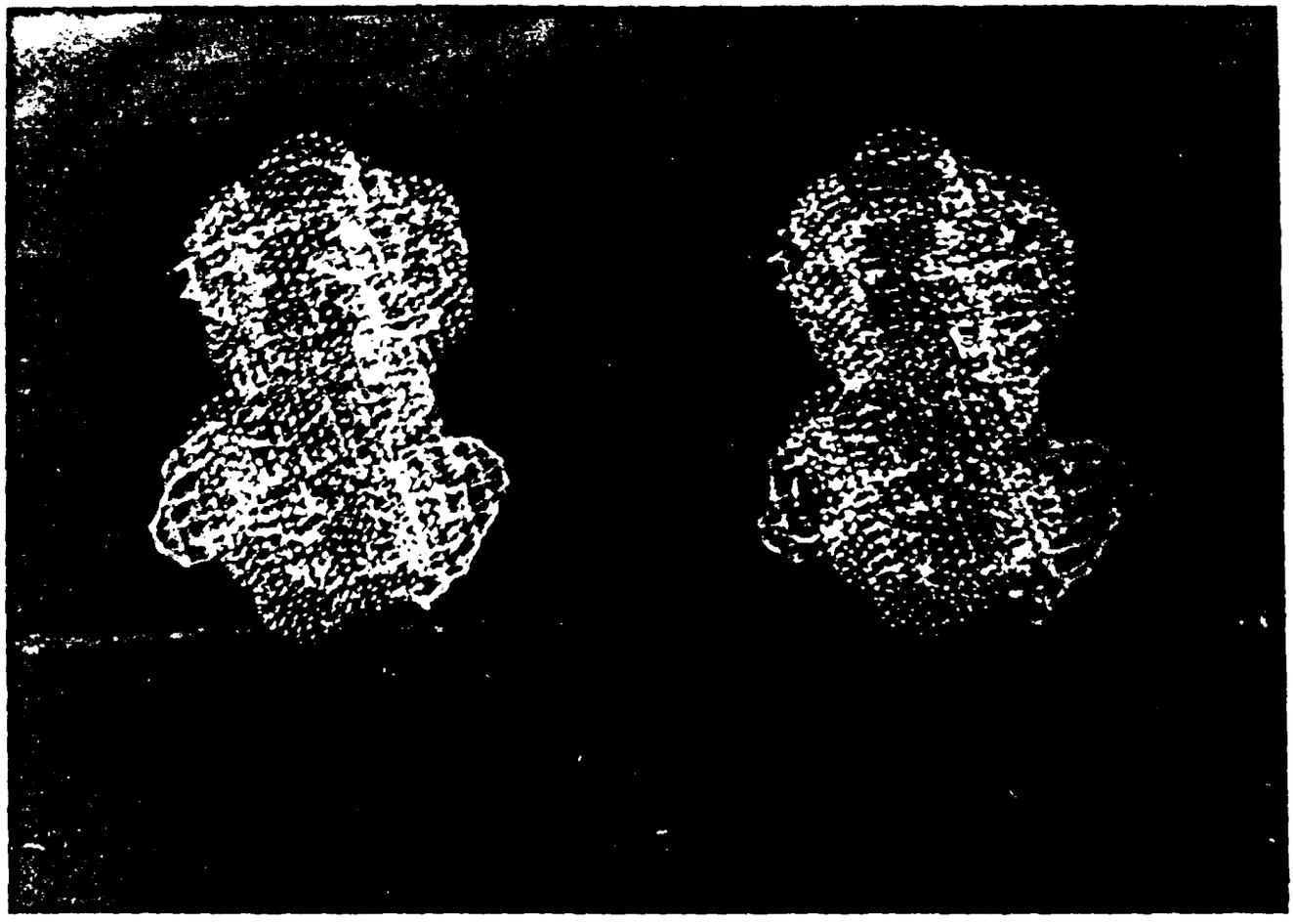
C. Receptor Map with Muscarine (green)



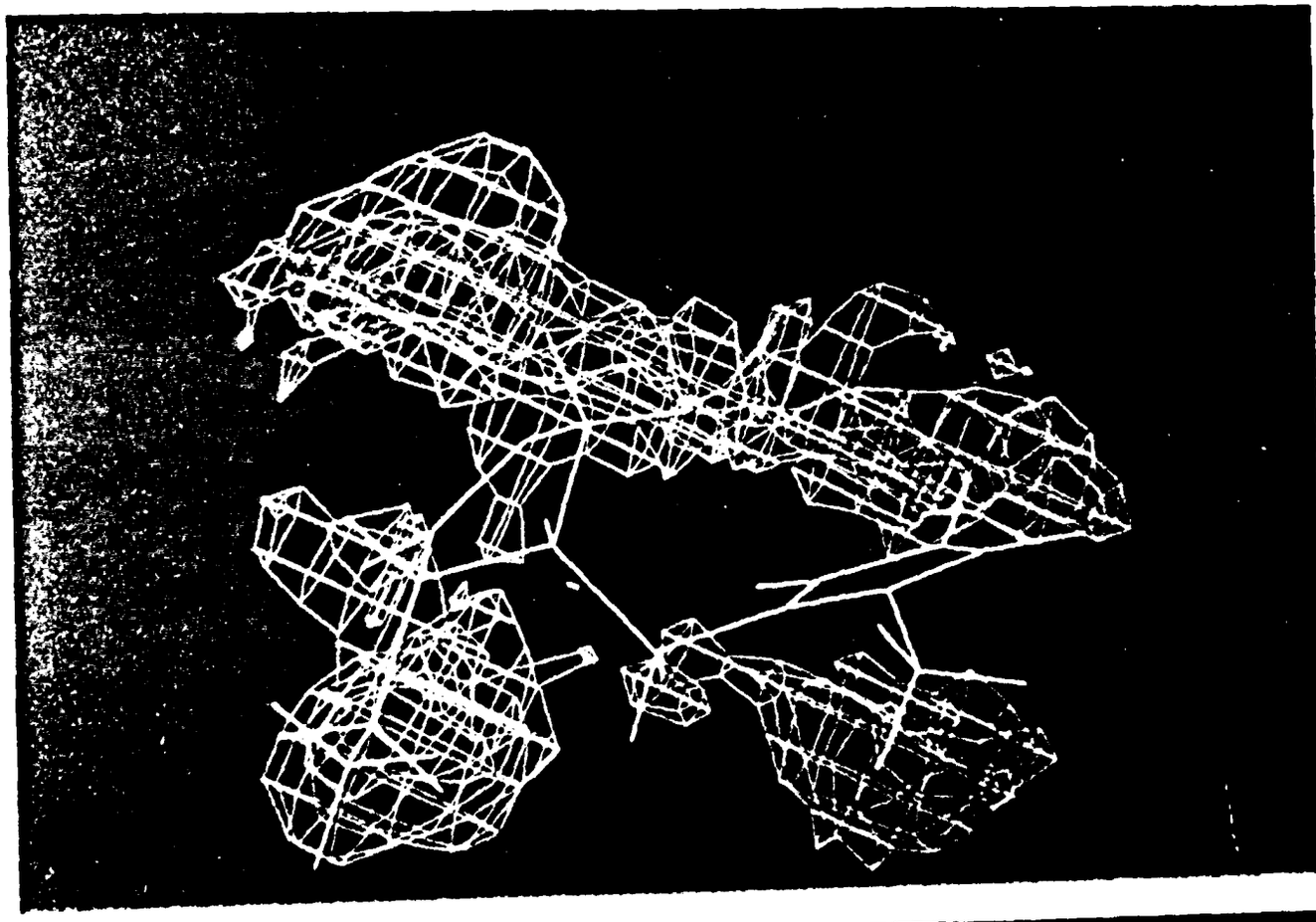
D. Receptor Map with Muscarine (dot structure)



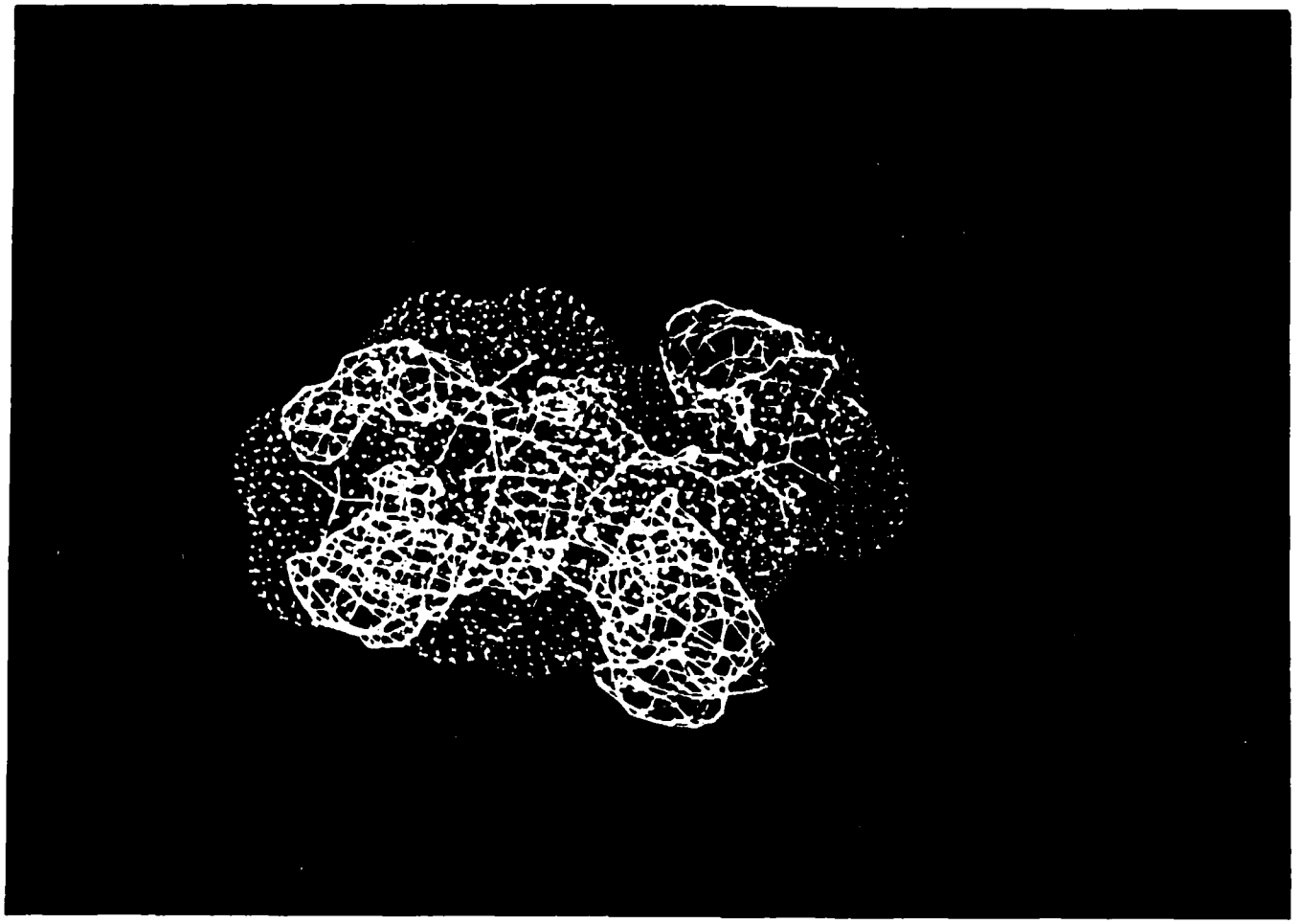
E. Receptor Map with Muscarine(stereo)



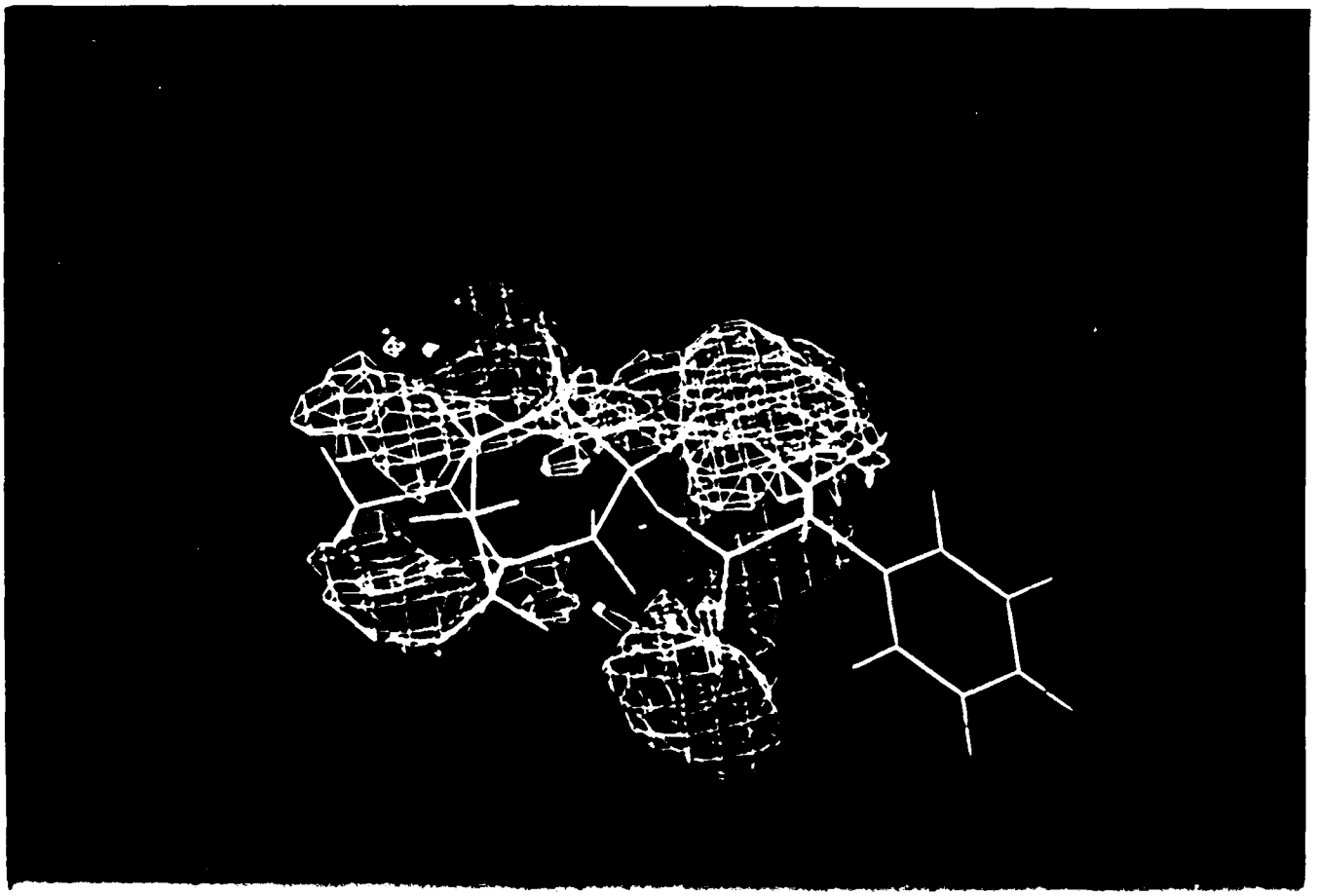
F. Receptor Map with Pilocarpine



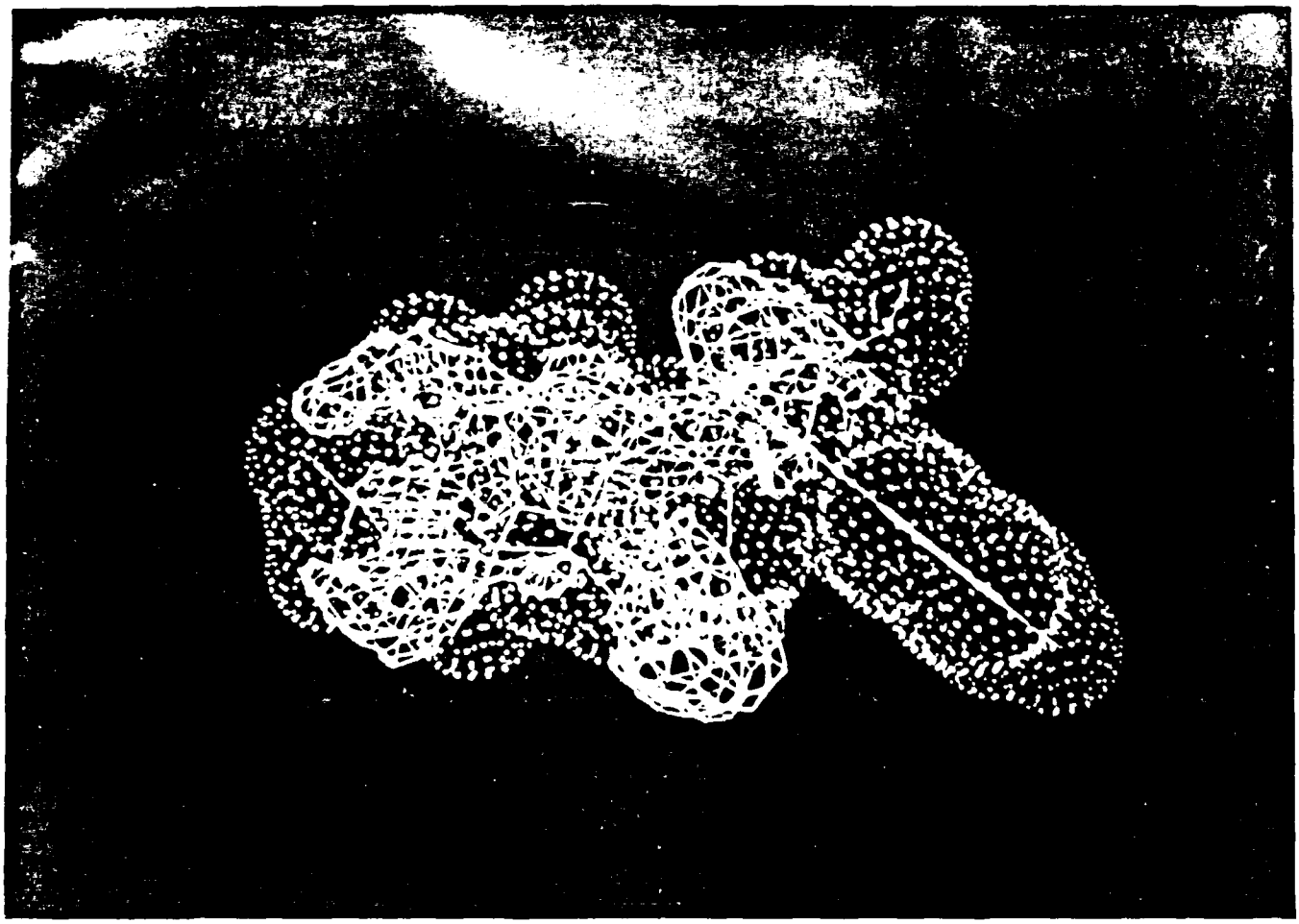
G. Receptor Map with Tropine (dot)



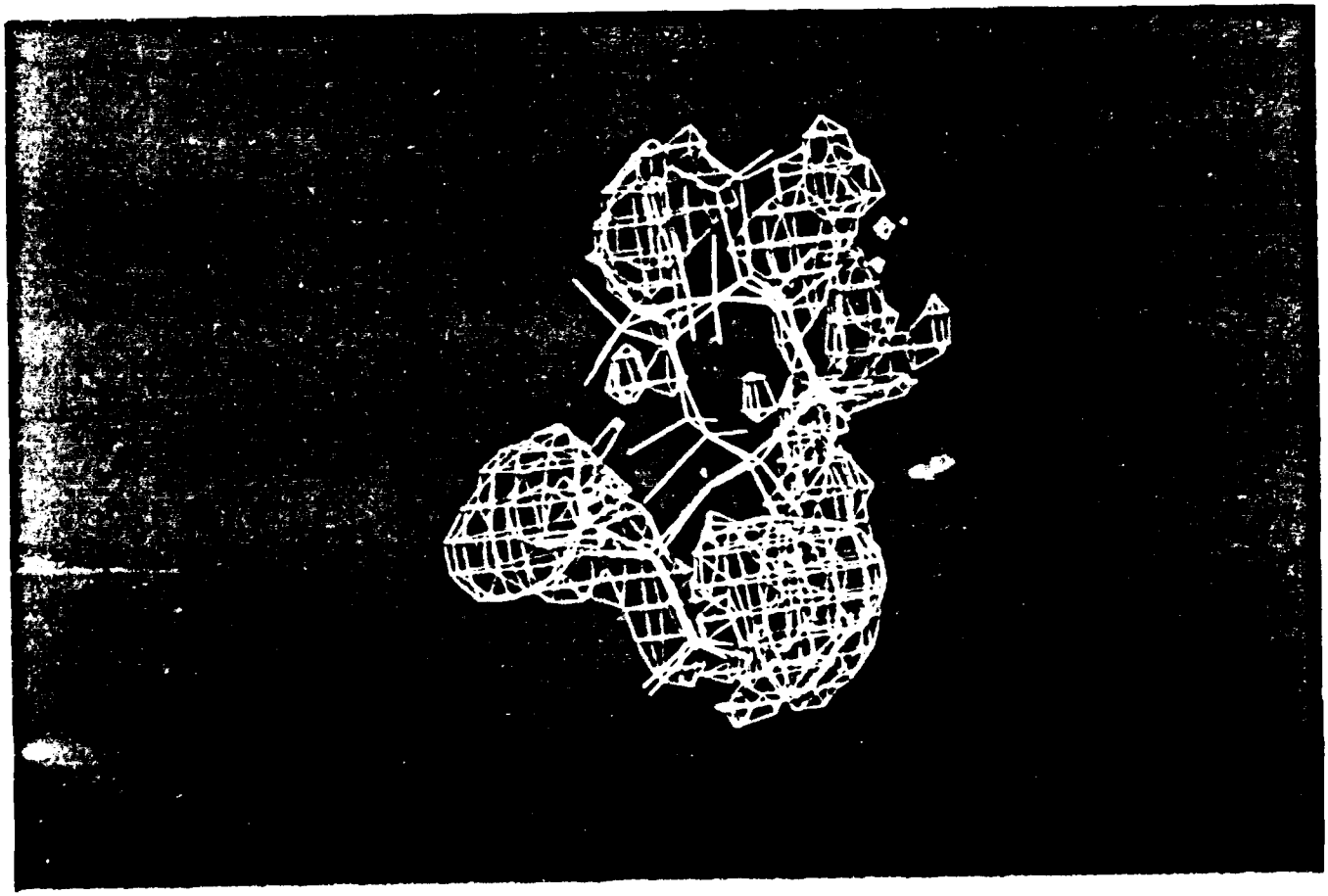
H. Receptor Map with Atropine



I. Receptor Map [illegible]



J. Receptor Map with Tropine and Rigid Analog xTropine



K. Fitting of Atropine and Rigid Analog xAtropine

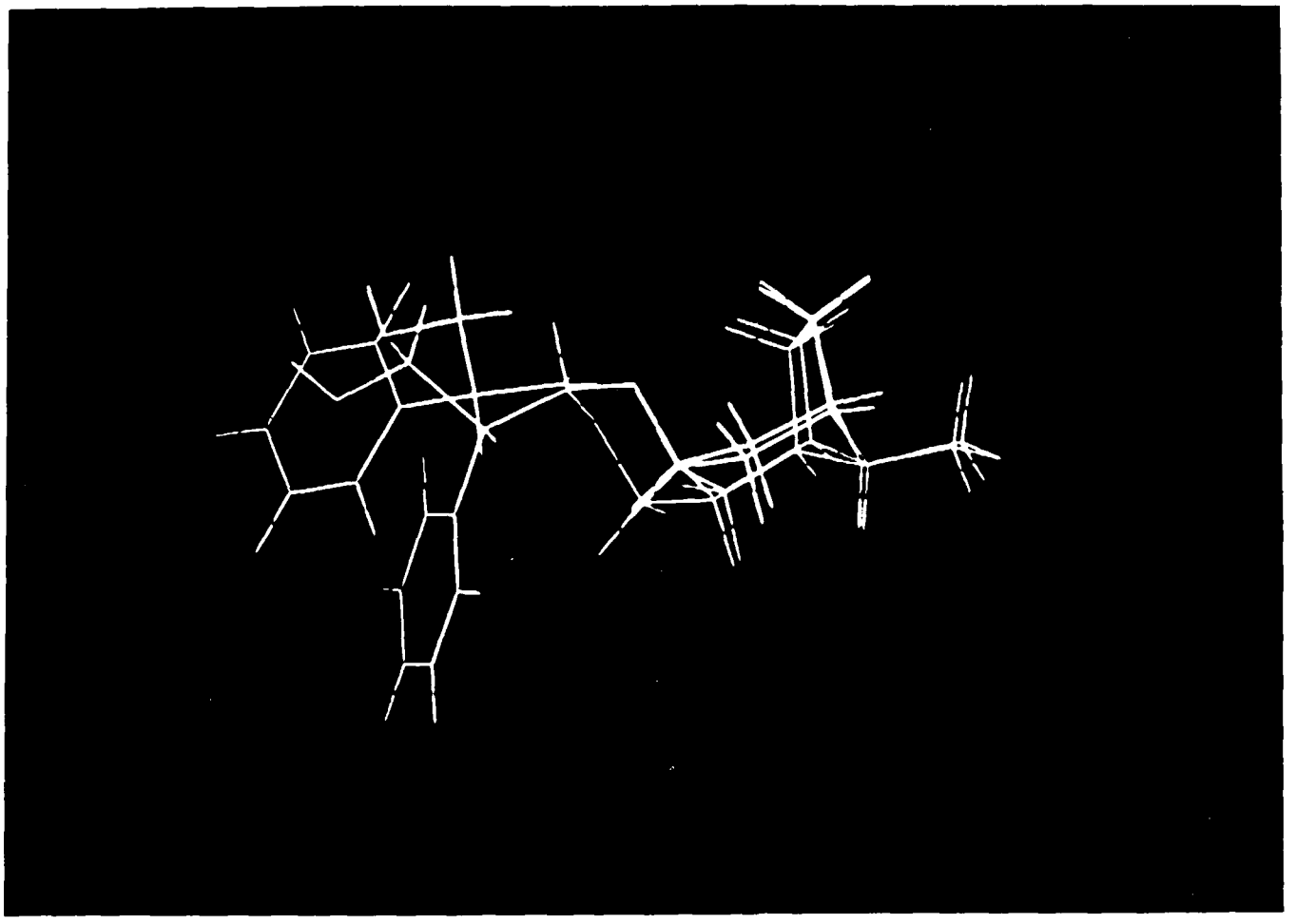
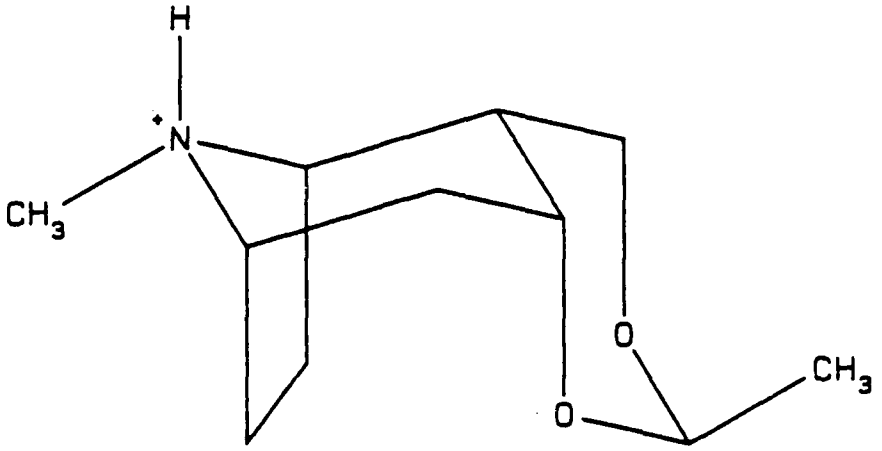
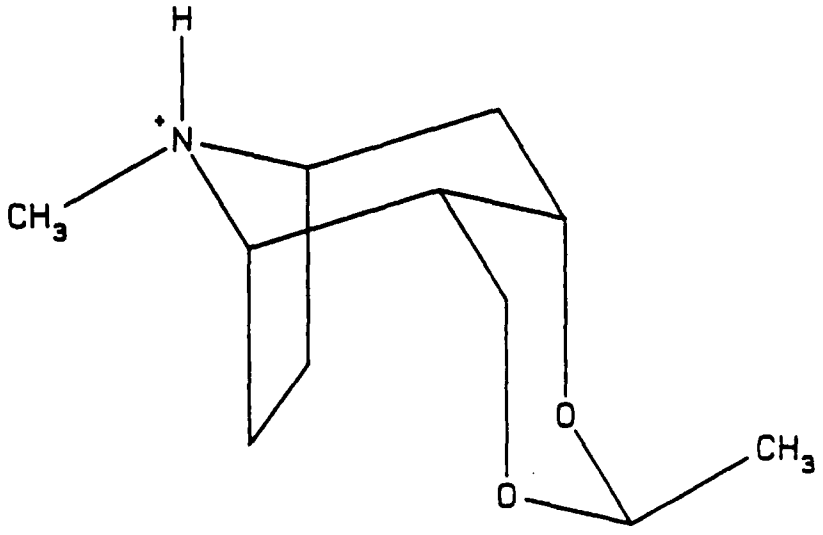


Chart XVII

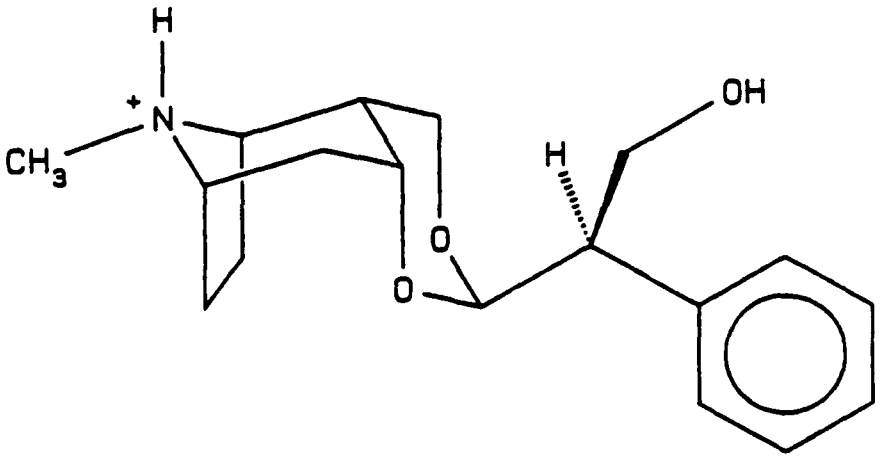


Xtropine-A

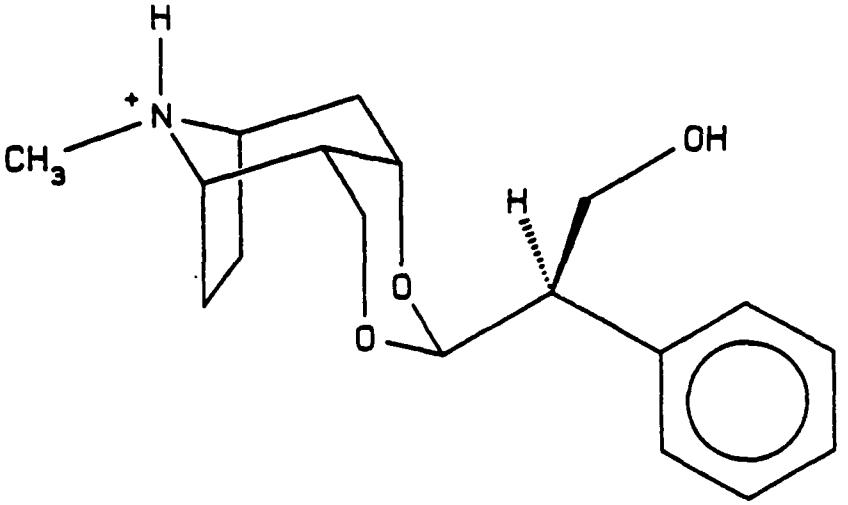


Xtropine-B

Chart XVIII



Xatropine-1



Xatropine-2

Table XXXIII

Pharmacophore Model for the Rigid Analogues of Tropine and Atropine

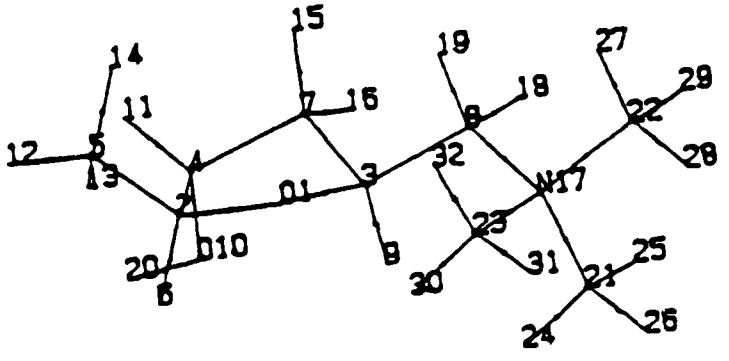
	Schulman Distance	Schulman Angle	Beers Distance	Conformational Energy
Xtropine-A	6.744	-156.551	4.402	23.06
Xtropine-B	6.751	156.713	4.410	23.06
Xatropine-1	6.702	-154.693	4.345	30.16
Xatropine-2	6.712	155.541	4.356	25.18

Appendix A. MNDO Charge Calculations

MNDO CHARGES - MUSCARINE (GLOBAL MINIMUM)

		x	y	z	charge
1	O	2.7422	-0.0747	3.5455	-0.3323
2	C	3.3868	-0.6266	2.4075	0.0776
3	C	3.6946	0.6787	4.2713	0.0911
4	C	4.7018	0.1445	2.2117	0.0931
5	C	2.4326	-0.5062	1.2161	0.0218
6	H	3.5771	-1.7024	2.6381	0.0449
7	C	4.5523	1.3220	3.1766	-0.0318
8	C	3.0029	1.7083	5.1821	0.0690
9	H	4.3124	-0.0425	4.8560	0.0393
10	O	5.7831	-0.6459	2.6585	-0.3187
11	H	4.9139	0.4595	1.1620	0.0485
12	H	2.8842	-0.9503	0.2994	0.0179
13	H	1.4733	-1.0373	1.4156	0.0205
14	H	2.1953	0.5615	1.0029	0.0063
15	H	3.9937	2.1510	2.6805	0.0348
16	H	5.5262	1.7135	3.5542	0.0608
17	N	2.2504	1.1917	6.3811	-0.0833
18	H	3.7898	2.4165	5.5339	0.0609
19	H	2.3084	2.3042	4.5440	0.0708
20	H	6.0820	-1.1921	1.9475	0.1955
21	C	3.1692	0.4891	7.3330	0.0813
22	C	1.6331	2.3620	7.0899	0.0826
23	C	1.1592	0.2522	5.9698	0.0861
24	H	3.6022	-0.4332	6.8858	0.0666
25	H	4.0083	1.1541	7.6419	0.0592
26	H	2.6242	0.1761	8.2533	0.0593
27	H	0.9236	2.9056	6.4242	0.0622
28	H	1.0656	2.0345	7.9914	0.0615
29	H	2.4127	3.0843	7.4256	0.0592
30	H	1.5694	-0.6846	5.5313	0.0785
31	H	0.5443	-0.0508	6.8484	0.0505
32	H	0.4807	0.7288	5.2253	0.0662

$



MNDO CHARGES - MUSCARINE (150°dihed. angle)

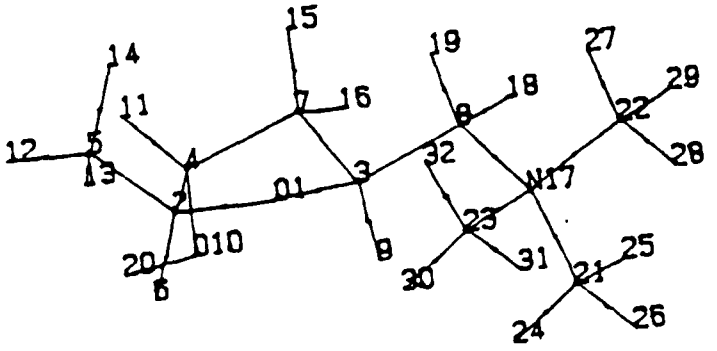
		x	y	z	charge
1	O	1.6252	-0.0408	-1.1411	-0.3032
2	C	1.9266	-0.5316	-2.4385	0.0750
3	C	0.2172	-0.0406	-0.9814	0.0973
4	C	0.6680	-1.2437	-2.9580	0.0927
5	C	3.1428	-1.4558	-2.3318	0.0225
6	H	2.1771	0.3577	-3.0657	0.0461
7	C	-0.2273	-1.3083	-1.7178	-0.0421
8	C	-0.1237	0.0271	0.5208	0.0595
9	H	-0.1354	0.8679	-1.5216	0.0305
10	O	0.0267	-0.4342	-3.9215	-0.3216
11	H	0.8498	-2.2436	-3.4197	0.0469
12	H	3.4321	-1.8483	-3.3337	0.0149
13	H	4.0216	-0.9152	-1.9105	0.0266
14	H	2.9248	-2.3249	-1.6693	0.0058
15	H	0.0254	-2.2155	-1.1198	0.0366
16	H	-1.3115	-1.3352	-1.9724	0.0448
17	N	-1.4082	0.7046	0.9243	-0.0854
18	H	-0.1067	-1.0128	0.9222	0.0665
19	H	0.7144	0.5568	1.0324	0.0790
20	H	0.4594	-0.5498	-4.7542	0.1963
21	C	-2.5850	0.0593	0.2637	0.0795
22	C	-1.5614	0.5771	2.4125	0.0835
23	C	-1.3841	2.1634	0.5791	0.0812
24	H	-2.5575	0.2075	-0.8388	0.0652
25	H	-2.6098	-1.0347	0.4746	0.0613
26	H	-3.5403	0.5030	0.6274	0.0607
27	H	-0.7074	1.0541	2.9468	0.0647
28	H	-2.4979	1.0677	2.7653	0.0616
29	H	-1.6065	-0.4929	2.7212	0.0617
30	H	-1.3397	2.3325	-0.5194	0.0672
31	H	-2.3050	2.6731	0.9454	0.0588
32	H	-0.5066	2.6696	1.0433	0.0659

```
$ T MUS180N.OUT
```

MNDO CHARGES - MUSCARINE (GLOBAL MINIMUM)

		x	y	z	charge
1	O	2.7422	-0.0747	3.5455	-0.3323
2	C	3.3868	-0.6266	2.4075	0.0776
3	C	3.6946	0.6787	4.2713	0.0911
4	C	4.7018	0.1445	2.2117	0.0931
5	C	2.4326	-0.5062	1.2161	0.0218
6	H	3.5771	-1.7024	2.6381	0.0449
7	C	4.5523	1.3220	3.1766	-0.0318
8	C	3.0029	1.7083	5.1821	0.0690
9	H	4.3124	-0.0425	4.8560	0.0393
10	O	5.7831	-0.6459	2.6585	-0.3187
11	H	4.9139	0.4595	1.1620	0.0485
12	H	2.8842	-0.9503	0.2994	0.0179
13	H	1.4733	-1.0373	1.4156	0.0205
14	H	2.1953	0.5615	1.0029	0.0063
15	H	3.9937	2.1510	2.6805	0.0348
16	H	5.5262	1.7135	3.5542	0.0608
17	N	2.2504	1.1917	6.3811	-0.0833
18	H	3.7898	2.4165	5.5339	0.0609
19	H	2.3084	2.3042	4.5440	0.0708
20	H	6.0820	-1.1921	1.9475	0.1955
21	C	3.1692	0.4891	7.3330	0.0813
22	C	1.6331	2.3620	7.0899	0.0826
23	C	1.1592	0.2522	5.9698	0.0861
24	H	3.6022	-0.4332	6.8858	0.0666
25	H	4.0083	1.1541	7.6419	0.0592
26	H	2.6242	0.1761	8.2533	0.0593
27	H	0.9236	2.9056	6.4242	0.0622
28	H	1.0656	2.0345	7.9914	0.0615
29	H	2.4127	3.0843	7.4256	0.0592
30	H	1.5694	-0.6846	5.5313	0.0785
31	H	0.5443	-0.0508	6.8484	0.0505
32	H	0.4807	0.7288	5.2253	0.0662

$



MNDO CHARGES - MUSCARINE (150°dihed. angle)

		x	y	z	charge
1	O	1.6252	-0.0408	-1.1411	-0.3032
2	C	1.9266	-0.5316	-2.4385	0.0750
3	C	0.2172	-0.0406	-0.9814	0.0973
4	C	0.6680	-1.2437	-2.9580	0.0927
5	C	3.1428	-1.4558	-2.3318	0.0225
6	H	2.1771	0.3577	-3.0657	0.0461
7	C	-0.2273	-1.3083	-1.7178	-0.0421
8	C	-0.1237	0.0271	0.5208	0.0595
9	H	-0.1354	0.8679	-1.5216	0.0305
10	O	0.0267	-0.4342	-3.9215	-0.3216
11	H	0.8498	-2.2436	-3.4197	0.0469
12	H	3.4321	-1.8483	-3.3337	0.0149
13	H	4.0216	-0.9152	-1.9105	0.0266
14	H	2.9248	-2.3249	-1.6693	0.0058
15	H	0.0254	-2.2155	-1.1198	0.0366
16	H	-1.3115	-1.3352	-1.9724	0.0448
17	N	-1.4082	0.7046	0.9243	-0.0854
18	H	-0.1067	-1.0128	0.9222	0.0665
19	H	0.7144	0.5568	1.0324	0.0790
20	H	0.4594	-0.5498	-4.7542	0.1963
21	C	-2.5850	0.0593	0.2637	0.0795
22	C	-1.5614	0.5771	2.4125	0.0835
23	C	-1.3841	2.1634	0.5791	0.0812
24	H	-2.5575	0.2075	-0.8388	0.0652
25	H	-2.6098	-1.0347	0.4746	0.0613
26	H	-3.5403	0.5030	0.6274	0.0607
27	H	-0.7074	1.0541	2.9468	0.0647
28	H	-2.4979	1.0677	2.7653	0.0616
29	H	-1.6065	-0.4929	2.7212	0.0617
30	H	-1.3397	2.3325	-0.5194	0.0672
31	H	-2.3050	2.6731	0.9454	0.0588
32	H	-0.5066	2.6696	1.0433	0.0659

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$ T MUS180N.OUT
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MNDO CHARGE - MUSCARINE (180^{O} dihe. angle)

		x	y	z	charge
1	O	1.6284	-0.0788	-1.0983	-0.3046
2	C	1.9776	-0.4788	-2.4127	0.0761
3	C	0.2147	-0.0371	-0.9938	0.0986
4	C	0.7363	-1.1464	-3.0198	0.0944
5	C	3.1869	-1.4137	-2.3242	0.0233
6	H	2.2516	0.4514	-2.9663	0.0473
7	C	-0.2307	-1.2336	-1.8363	-0.0468
8	C	-0.1361	-0.0295	0.5075	0.0580
9	H	-0.0991	0.9205	-1.4753	0.0387
10	O	0.1616	-0.2898	-3.9842	-0.3201
11	H	0.9219	-2.1332	-3.5074	0.0457
12	H	3.5110	-1.7396	-3.3392	0.0149
13	H	4.0512	-0.9066	-1.8365	0.0274
14	H	2.9431	-2.3240	-1.7296	0.0046
15	H	-0.0658	-2.1833	-1.2745	0.0306
16	H	-1.2879	-1.1724	-2.1819	0.0442
17	N	-1.5800	0.0141	0.9373	-0.0841
18	H	0.3536	-0.9129	0.9810	0.0727
19	H	0.3804	0.8662	0.9280	0.0739
20	H	0.6494	-0.3647	-4.7906	0.1965
21	C	-2.2921	-1.2748	0.6663	0.0804
22	C	-1.6163	0.2494	2.4212	0.0829
23	C	-2.2992	1.1352	0.2547	0.0797
24	H	-2.4112	-1.4670	-0.4194	0.0629
25	H	-1.7501	-2.1362	1.1200	0.0634
26	H	-3.3223	-1.2571	1.0911	0.0596
27	H	-1.1287	1.2148	2.6903	0.0643
28	H	-2.6642	0.2924	2.7986	0.0613
29	H	-1.0902	-0.5666	2.9688	0.0637
30	H	-2.3530	0.9694	-0.8451	0.0652
31	H	-3.3463	1.2221	0.6260	0.0600
32	H	-1.7865	2.1076	0.4379	0.0654

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MNDO CHARGES - EPTALLOMUSCARINE (70°) (GLOBAL MIN.)

		x	y	z	charge
1	O	1.6212	-0.0344	-1.1745	-0.3305
2	C	1.9218	-0.8155	-2.3205	0.0818
3	C	0.2180	-0.0221	-0.9776	0.0925
4	C	0.5890	-1.2577	-2.9372	0.0938
5	C	2.8491	-0.0288	-3.2487	0.0229
6	H	2.4568	-1.7136	-1.9269	0.0324
7	C	-0.3101	-1.2668	-1.7011	-0.0327
8	C	-0.1302	0.0103	0.5209	0.0653
9	H	-0.1621	0.8857	-1.5009	0.0408
10	O	0.1014	-0.2783	-3.8285	-0.3176
11	H	0.6271	-2.2362	-3.4740	0.0511
12	H	3.0828	-0.6187	-4.1646	0.0137
13	H	2.3869	0.9347	-3.5630	0.0160
14	H	3.8112	0.2118	-2.7402	0.0193
15	H	-0.1238	-2.1857	-1.0959	0.0344
16	H	-1.3968	-1.2047	-1.9457	0.0603
17	N	0.1618	1.2765	1.2842	-0.0824
18	H	-1.2192	-0.2147	0.6102	0.0600
19	H	0.4055	-0.8410	1.0034	0.0691
20	H	0.4251	-0.4612	-4.6975	0.1965
21	C	-0.6358	2.4260	0.7483	0.0813
22	C	-0.2201	1.0596	2.7195	0.0827
23	C	1.6179	1.6208	1.2235	0.0859
24	H	-0.3411	2.6859	-0.2926	0.0678
25	H	-1.7255	2.1930	0.7548	0.0587
26	H	-0.4780	3.3407	1.3651	0.0590
27	H	0.3646	0.2236	3.1683	0.0619
28	H	-0.0278	1.9714	3.3308	0.0614
29	H	-1.3028	0.8122	2.8135	0.0590
30	H	1.9315	1.8938	0.1914	0.0800
31	H	1.8447	2.5011	1.8680	0.0503
32	H	2.2449	0.7690	1.5745	0.0654

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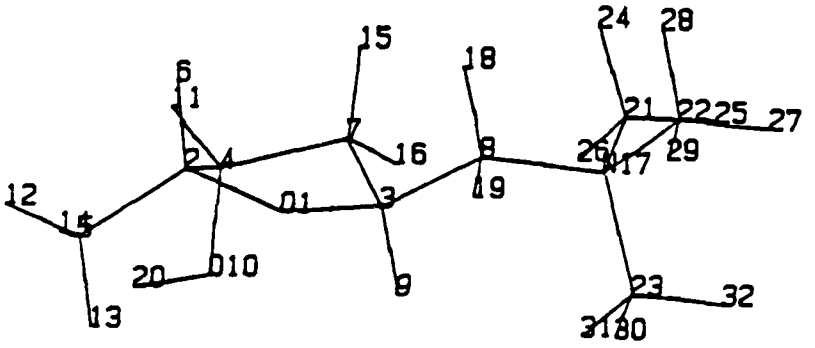

MNDO CHARGES - EPIALLOMUSCARINE (150°)

		x	y	z	charge
1	O	1.6226	-0.0334	-1.1483	-0.3010
2	C	1.9646	-0.8030	-2.2898	0.0790
3	C	0.2128	-0.0361	-0.9870	0.0987
4	C	0.6543	-1.2525	-2.9473	0.0936
5	C	2.9122	-0.0022	-3.1851	0.0229
6	H	2.4953	-1.6994	-1.8869	0.0337
7	C	-0.2847	-1.2762	-1.7407	-0.0443
8	C	-0.1228	0.0274	0.5160	0.0550
9	H	-0.1219	0.8867	-1.5135	0.0348
10	O	0.1801	-0.2755	-3.8485	-0.3201
11	H	0.7176	-2.2268	-3.4891	0.0493
12	H	3.1776	-0.5838	-4.0976	0.0103
13	H	2.4514	0.9596	-3.5067	0.0160
14	H	3.8572	0.2425	-2.6474	0.0260
15	H	-0.1127	-2.2021	-1.1427	0.0349
16	H	-1.3568	-1.2339	-2.0404	0.0449
17	N	-1.4064	0.7020	0.9262	-0.0846
18	H	-0.1051	-1.0149	0.9110	0.0642
19	H	0.7168	0.5534	1.0290	0.0795
20	H	0.5989	-0.4016	-4.6867	0.1973
21	C	-2.5855	0.0704	0.2572	0.0798
22	C	-1.5613	0.5581	2.4126	0.0836
23	C	-1.3759	2.1644	0.5967	0.0811
24	H	-2.5634	0.2415	-0.8418	0.0646
25	H	-2.6111	-1.0272	0.4480	0.0609
26	H	-3.5390	0.5084	0.6324	0.0603
27	H	-0.7051	1.0243	2.9529	0.0647
28	H	-2.4953	1.0497	2.7706	0.0613
29	H	-1.6123	-0.5152	2.7087	0.0613
30	H	-1.3277	2.3451	-0.4998	0.0679
31	H	-2.2958	2.6735	0.9662	0.0582
32	H	-0.4981	2.6627	1.0687	0.0660

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MNDO CHARGES - EPIALLOMUSCARINE (162° dihed. angle)

		x	y	z	charge
1	O	2.0531	0.4023	2.3694	-0.2963
2	C	3.2107	0.3144	1.5583	0.0796
3	C	2.4190	0.2999	3.7393	0.0996
4	C	4.3090	-0.2884	2.4353	0.0950
5	C	2.8903	-0.4592	0.2784	0.0264
6	H	3.4795	1.3688	1.3043	0.0227
7	C	3.9531	0.3316	3.7864	-0.0454
8	C	1.6719	1.4069	4.5097	0.0487
9	H	2.0540	-0.7106	4.0352	0.0429
10	O	4.1550	-1.6848	2.5396	-0.3150
11	H	5.3499	-0.0705	2.0948	0.0486
12	H	3.7992	-0.5599	-0.3580	0.0104
13	H	2.5101	-1.4813	0.5051	0.0197
14	H	2.1090	0.0648	-0.3191	0.0257
15	H	4.3274	1.3813	3.8346	0.0260
16	H	4.3961	-0.2531	4.6249	0.0481
17	N	1.5378	1.2970	6.0065	-0.0837
18	H	2.1531	2.3791	4.2506	0.0645
19	H	0.6429	1.4579	4.0807	0.0777
20	H	4.5684	-2.1000	1.7969	0.1971
21	C	2.8712	1.2954	6.6838	0.0805
22	C	0.7625	2.4876	6.4941	0.0832
23	C	0.7901	0.0558	6.3876	0.0809
24	H	3.4788	2.1767	6.3743	0.0618
25	H	2.7560	1.3284	7.7917	0.0600
26	H	3.4400	0.3690	6.4551	0.0621
27	H	0.6249	2.4554	7.5996	0.0611
28	H	1.2902	3.4379	6.2476	0.0619
29	H	-0.2508	2.5260	6.0315	0.0649
30	H	-0.2046	0.0181	5.8867	0.0666
31	H	1.3535	-0.8641	6.1139	0.0660
32	H	0.6208	0.0158	7.4883	0.0587

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MNDO CHARGES - EPIALLOMUSCARINE (180°)

		x	y	z	charges
1	O	1.6363	-0.0507	-1.1094	-0.3004
2	C	2.0196	-0.8341	-2.2263	0.0807
3	C	0.2196	-0.0228	-0.9995	0.1003
4	C	0.7412	-1.1674	-2.9988	0.0958
5	C	3.1026	-0.1039	-3.0224	0.0239
6	H	2.4397	-1.7745	-1.7937	0.0281
7	C	-0.2801	-1.1867	-1.8613	-0.0486
8	C	-0.1283	-0.0195	0.5025	0.0521
9	H	-0.0827	0.9459	-1.4650	0.0443
10	O	0.3962	-0.1196	-3.8784	-0.3170
11	H	0.7856	-2.1172	-3.5844	0.0484
12	H	3.4003	-0.6968	-3.9175	0.0098
13	H	2.7496	0.8945	-3.3679	0.0188
14	H	4.0129	0.0592	-2.4006	0.0266
15	H	-0.2088	-2.1497	-1.3024	0.0266
16	H	-1.3145	-1.0437	-2.2511	0.0454
17	N	-1.5710	0.0108	0.9380	-0.0839
18	H	0.3653	-0.9061	0.9658	0.0688
19	H	0.3868	0.8739	0.9298	0.0757
20	H	0.8810	-0.2194	-4.6838	0.1978
21	C	-2.2863	-1.2711	0.6436	0.0810
22	C	-1.6015	0.2166	2.4265	0.0828
23	C	-2.2916	1.1464	0.2810	0.0799
24	H	-2.4195	-1.4356	-0.4452	0.0618
25	H	-1.7398	-2.1430	1.0708	0.0631
26	H	-3.3118	-1.2634	1.0798	0.0594
27	H	-1.1108	1.1754	2.7131	0.0645
28	H	-2.6479	0.2543	2.8085	0.0609
29	H	-1.0754	-0.6113	2.9558	0.0633
30	H	-2.3446	1.0058	-0.8223	0.0645
31	H	-3.3387	1.2239	0.6544	0.0594
32	H	-1.7799	2.1150	0.4855	0.0660

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[illegible] dihed.angle) (Global Min.)

		x	y	z	charge
1	O	1.6329	-0.0365	-1.1291	-0.4026
2	C	2.1155	-1.1079	-1.9167	0.6865
3	C	0.2225	-0.0222	-0.9766	0.1505
4	C	2.1815	-2.2962	-0.9573	0.1928
5	C	2.2255	-2.3675	-1.0563	0.4360
6	H	2.1763	-1.9974	-1.2430	-0.9004
7	C	-0.3179	-1.2854	-1.6739	-0.5285
8	C	-0.1317	0.0139	0.5253	0.0540
9	H	-0.1533	0.8854	-1.5036	0.0360
10	O	3.2648	-2.1434	-0.0650	-0.3112
11	H	2.2576	-3.2940	-1.4528	-0.0174
12	H	2.5537	-3.2361	-1.6720	0.0568
13	H	2.9676	-2.2257	-0.2371	0.0799
14	H	1.2501	-2.6258	-0.5844	0.3726
15	H	-1.1415	-1.7945	-1.1211	0.0097
16	H	-0.6974	-1.0306	-2.6927	0.0432
17	N	0.2591	1.2314	1.3242	-0.0850
18	H	-1.2381	-0.1079	0.5996	0.0688
19	H	0.3145	-0.8896	1.0025	0.0429
20	H	4.0092	-2.6130	-0.4128	0.2095
21	C	-0.3835	2.4670	0.7751	0.0838
22	C	-0.2102	1.0329	2.7365	0.0821
23	C	1.7452	1.4174	1.3433	0.0836
24	H	-0.0132	2.7032	-0.2474	0.0673
25	H	-1.4910	2.3536	0.7284	0.0599
26	H	-0.1560	3.3512	1.4143	0.0575
27	H	-1.3165	0.9045	2.7783	0.0597
28	H	0.2593	0.1307	3.1926	0.0581
29	H	0.0500	1.9082	3.3755	0.0607
30	H	2.1399	1.6932	0.3407	0.0801
31	H	2.0319	2.2472	2.0298	0.0505
32	H	2.2608	0.4925	1.6908	0.0627

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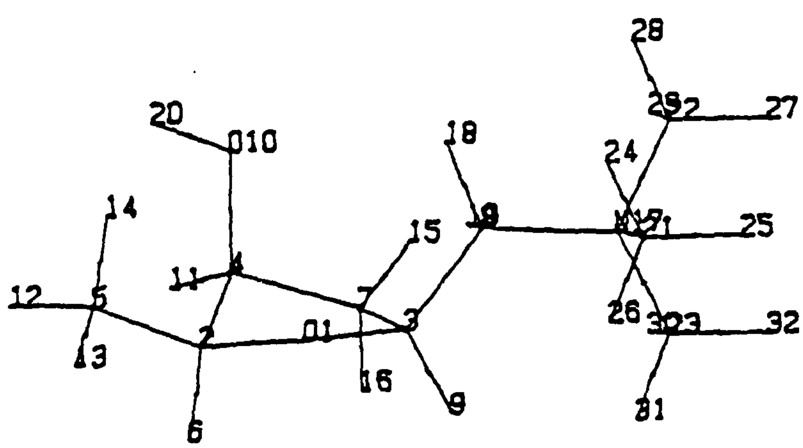

MNDO CHARGES - EPIMUSCARINE (150°)

		x	y	z	charge
1	O	1.6530	-0.0834	-1.0085	-0.3690
2	C	2.1565	-1.1892	-1.7333	0.6838
3	C	0.2339	-0.0719	-0.9264	0.1551
4	C	2.1652	-2.3454	-0.7331	0.1998
5	C	2.2117	-2.4190	-0.8255	0.4358
6	H	2.1738	-2.0522	-1.0235	-0.8919
7	C	-0.2708	-1.3490	-1.6212	-0.5706
8	C	-0.1422	0.0392	0.5681	0.0478
9	H	-0.0757	0.8324	-1.4977	0.0268
10	O	3.2156	-2.1871	0.1964	-0.3224
11	H	2.2424	-3.3604	-1.1920	-0.0210
12	H	2.5546	-3.3127	-1.3957	0.0608
13	H	2.9196	-2.2580	0.0200	0.0864
14	H	1.2134	-2.6493	-0.3884	0.3877
15	H	-1.1243	-1.8499	-1.1103	-0.0072
16	H	-0.5824	-1.1207	-2.6687	0.0390
17	N	-1.4308	0.7377	0.9196	-0.0803
18	H	-0.1459	-0.9884	0.9998	0.0437
19	H	0.6859	0.5751	1.0896	0.0675
20	H	3.9975	-2.5793	-0.1654	0.2177
21	C	-2.5982	0.0900	0.2455	0.0835
22	C	-1.6246	0.6493	2.4059	0.0829
23	C	-1.3785	2.1863	0.5379	0.0828
24	H	-2.5195	0.1711	-0.8622	0.0743
25	H	-2.6707	-0.9870	0.5214	0.0615
26	H	-3.5531	0.5807	0.5439	0.0548
27	H	-1.6873	-0.4118	2.7411	0.0583
28	H	-0.7810	1.1328	2.9508	0.0622
29	H	-2.5658	1.1567	2.7202	0.0613
30	H	-1.3066	2.3251	-0.5634	0.0679
31	H	-2.3004	2.7178	0.8689	0.0575
32	H	-0.5056	2.6936	1.0096	0.0634

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MNDO CHARGES - EPIMUSCARINE (180° dihed. angle)

		x	y	z	charge
1	O	1.6596	-0.3016	-0.7886	-0.2931
2	C	2.0717	-0.9451	-1.9785	0.0815
3	C	0.2398	-0.2653	-0.7968	0.0997
4	C	1.1236	-2.1396	-2.0864	0.0977
5	C	3.5618	-1.2816	-1.8959	0.0315
6	H	1.8914	-0.2309	-2.8194	0.0224
7	C	-0.1579	-1.6112	-1.4259	-0.0491
8	C	-0.2223	0.0097	0.6493	0.0594
9	H	-0.0394	0.5835	-1.4667	0.0232
10	O	1.6014	-3.2170	-1.3095	-0.3133
11	H	0.9755	-2.5051	-3.1310	0.0415
12	H	3.8851	-1.8554	-2.7946	0.0107
13	H	4.1754	-0.3528	-1.8430	0.0244
14	H	3.7972	-1.8883	-0.9920	0.0234
15	H	-0.4909	-2.3472	-0.6601	0.0385
16	H	-0.9714	-1.4744	-2.1773	0.0316
17	N	-1.6944	0.1118	0.9627	-0.0854
18	H	0.2175	-0.7925	1.2878	0.0781
19	H	0.2746	0.9583	0.9644	0.0754
20	H	2.2430	-3.6997	-1.8084	0.1946
21	C	-2.4432	-1.1599	0.7165	0.0822
22	C	-1.8322	0.4525	2.4199	0.0829
23	C	-2.3154	1.2086	0.1541	0.0796
24	H	-2.5154	-1.3907	-0.3681	0.0607
25	H	-1.9686	-2.0152	1.2501	0.0690
26	H	-3.4941	-1.0780	1.0779	0.0578
27	H	-1.3920	-0.3460	3.0609	0.0655
28	H	-1.3182	1.4114	2.6619	0.0638
29	H	-2.9023	0.5682	2.7093	0.0607
30	H	-2.2760	0.9780	-0.9346	0.0597
31	H	-3.3874	1.3477	0.4253	0.0604
32	H	-1.7905	2.1771	0.3227	0.0648

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MNDO CHARGES - EPIMUSCARINE (210° dihed.angle)

		x	y	z	charge
1	O	1.6411	-0.0270	-1.0824	-0.2951
2	C	1.9633	-0.4692	-2.3864	0.0813
3	C	0.2249	-0.0243	-0.9741	0.0979
4	C	1.0238	-1.6555	-2.6044	0.0982
5	C	3.4590	-0.7782	-2.4736	0.0315
6	H	1.7071	0.3615	-3.0893	0.0249
7	C	-0.2063	-1.2665	-1.7720	-0.0618
8	C	-0.1221	0.0132	0.5288	0.0613
9	H	-0.1176	0.9105	-1.4800	0.0378
10	O	1.5757	-2.8279	-2.0443	-0.3182
11	H	0.7962	-1.8592	-3.6785	0.0429
12	H	3.7155	-1.1986	-3.4730	0.0107
13	H	4.0639	0.1460	-2.3249	0.0259
14	H	3.7739	-1.5111	-1.6961	0.0218
15	H	-0.4675	-2.1196	-1.1063	0.0334
16	H	-1.0794	-1.0354	-2.4271	0.0364
17	N	-1.3973	-0.6232	1.0231	-0.0846
18	H	0.7351	-0.4519	1.0706	0.0848
19	H	-0.1239	1.0893	0.8254	0.0669
20	H	2.1805	-3.2122	-2.6607	0.1964
21	C	-1.4433	-2.1034	0.8101	0.0710
22	C	-1.4968	-0.3674	2.5007	0.0828
23	C	-2.5780	0.0041	0.3484	0.0794
24	H	-1.5307	-2.3609	-0.2674	0.0744
25	H	-0.5434	-2.5993	1.2413	0.0727
26	H	-2.3404	-2.5472	1.2999	0.0562
27	H	-0.6407	-0.8290	3.0452	0.0659
28	H	-1.4983	0.7247	2.7233	0.0620
29	H	-2.4363	-0.7928	2.9230	0.0607
30	H	-2.5701	-0.1978	-0.7466	0.0587
31	H	-3.5331	-0.4023	0.7541	0.0609
32	H	-2.5844	1.1085	0.4975	0.0627

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MNDO CHARGES - ALLOMUSCARINE (120° dihed angle)

		x	y	z	charge
1	C	1.6243	-0.0164	-1.1581	-0.3008
2	C	2.0913	-1.3379	-1.3801	0.0718
3	C	0.2156	-0.0269	-0.9888	0.1010
4	C	0.8711	-2.2661	-1.3607	0.0842
5	C	2.8407	-1.3616	-2.7169	0.0179
6	H	2.7963	-1.5768	-0.5482	0.0458
7	C	-0.2663	-1.3024	-1.6905	-0.0375
8	C	-0.1084	0.0227	0.5248	0.0417
9	H	-0.1583	0.8663	-1.5365	0.0383
10	O	0.6730	-2.7594	-0.0524	-0.3372
11	H	0.9322	-3.1381	-2.0551	0.0542
12	H	3.2511	-2.3766	-2.9240	0.0142
13	H	2.1690	-1.0831	-3.5609	0.0075
14	H	3.6942	-0.6451	-2.7094	0.0277
15	H	-1.2686	-1.6531	-1.3498	0.0452
16	H	-0.3120	-1.1413	-2.7942	0.0539
17	N	-0.9195	1.1939	1.0125	-0.0863
18	H	-0.6551	-0.9046	0.8098	0.0754
19	H	0.8498	-0.0134	1.0948	0.0803
20	H	1.1559	-3.5694	0.0366	0.2000
21	C	-2.2639	1.2177	0.3533	0.0828
22	C	-1.1170	1.0532	2.4943	0.0846
23	C	-0.1973	2.4805	0.7529	0.0824
24	H	-2.1829	1.3560	-0.7478	0.0597
25	H	-2.8146	0.2667	0.5376	0.0610
26	H	-2.8843	2.0558	0.7464	0.0595
27	H	-1.6583	0.1108	2.7412	0.0622
28	H	-0.1403	1.0386	3.0311	0.0637
29	H	-1.7143	1.9012	2.9021	0.0588
30	H	-0.0650	2.6749	-0.3342	0.0657
31	H	-0.7640	3.3444	1.1704	0.0552
32	H	0.8121	2.4722	1.2251	0.0670

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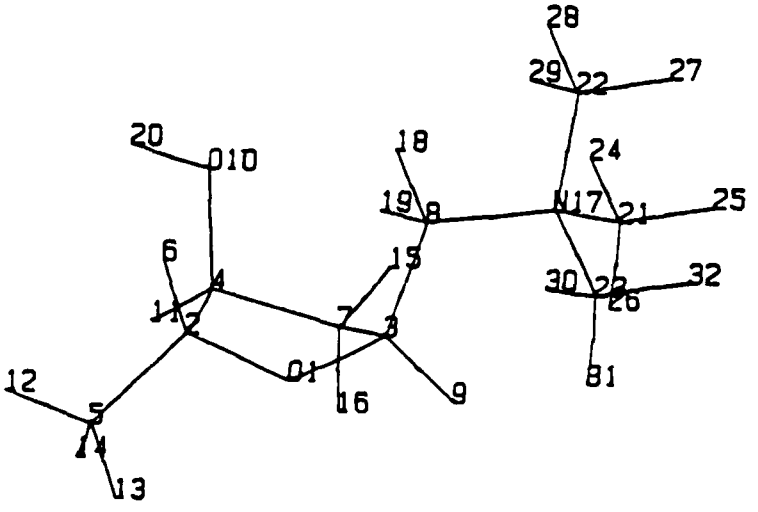

MNDO CHARGES - ALLOMUSCARINE (131° dihed. angle)

		x	y	z	charge
1	O	2.1100	-0.2461	3.2237	-0.2904
2	C	3.1140	0.1998	2.3268	0.0671
3	C	2.6288	-0.2013	4.5396	0.0954
4	C	4.4653	0.0662	3.0453	0.0869
5	C	3.0173	-0.6326	1.0459	0.0262
6	H	2.8828	1.2688	2.1018	0.0328
7	C	4.0993	-0.5984	4.3746	-0.0379
8	C	2.4002	1.2078	5.1351	0.0324
9	H	2.0753	-0.9896	5.0963	0.0445
10	O	4.9886	1.3508	3.3112	-0.3338
11	H	5.2385	-0.5069	2.4792	0.0511
12	H	3.7736	-0.2993	0.2985	0.0128
13	H	3.1934	-1.7120	1.2589	0.0138
14	H	2.0102	-0.5351	0.5787	0.0268
15	H	4.7442	-0.2867	5.2292	0.0425
16	H	4.1769	-1.7068	4.2649	0.0537
17	N	1.8044	1.2781	6.5161	-0.0843
18	H	3.3677	1.7591	5.1362	0.0813
19	H	1.7375	1.7796	4.4438	0.0744
20	H	5.5224	1.6173	2.5760	0.1995
21	C	2.6702	0.5536	7.4989	0.0821
22	C	1.7175	2.7208	6.9229	0.0838
23	C	0.4208	0.7021	6.5326	0.0823
24	H	3.7032	0.9716	7.5018	0.0629
25	H	2.2603	0.6416	8.5313	0.0600
26	H	2.7411	-0.5314	7.2609	0.0596
27	H	1.2806	2.8250	7.9429	0.0597
28	H	2.7254	3.1963	6.9392	0.0633
29	H	1.0760	3.2996	6.2189	0.0635
30	H	-0.2345	1.2169	5.7928	0.0664
31	H	0.4144	-0.3851	6.2989	0.0650
32	H	-0.0438	0.8173	7.5389	0.0569

$

MNDO CHARGES - ALLOMUSCARINE (150°)

		x	y	z	charge
1	O	1.6254	-0.0419	-1.1027	-0.2915
2	C	2.1042	-1.3549	-1.3434	0.0700
3	C	0.2144	-0.0533	-0.9624	0.1055
4	C	0.8940	-2.2926	-1.4107	0.0866
5	C	2.9129	-1.3316	-2.6448	0.0185
6	H	2.7724	-1.6149	-0.4878	0.0462
7	C	-0.2589	-1.3269	-1.6734	-0.0416
8	C	-0.1281	0.0495	0.5415	0.0336
9	H	-0.1320	0.8519	-1.5098	0.0377
10	O	0.6899	-2.9031	-0.1538	-0.3362
11	H	0.9729	-3.1041	-2.1734	0.0526
12	H	3.3433	-2.3358	-2.8636	0.0136
13	H	2.2744	-1.0343	-3.5081	0.0075
14	H	3.7576	-0.6075	-2.5787	0.0292
15	H	-1.2356	-1.7248	-1.3172	0.0370
16	H	-0.3395	-1.1385	-2.7708	0.0535
17	N	-1.4191	0.7255	0.9285	-0.0841
18	H	-0.1112	-0.9737	0.9783	0.0848
19	H	0.7052	0.5970	1.0421	0.0748
20	H	1.2303	-3.6794	-0.1082	0.2001
21	C	-2.5932	0.0654	0.2788	0.0821
22	C	-1.5758	0.6236	2.4185	0.0838
23	C	-1.3987	2.1777	0.5574	0.0817
24	H	-2.5521	0.1713	-0.8287	0.0580
25	H	-2.6340	-1.0180	0.5361	0.0658
26	H	-3.5482	0.5305	0.6154	0.0583
27	H	-1.6178	-0.4406	2.7473	0.0641
28	H	-0.7252	1.1135	2.9465	0.0634
29	H	-2.5151	1.1169	2.7597	0.0591
30	H	-1.3539	2.3267	-0.5440	0.0626
31	H	-2.3212	2.6916	0.9135	0.0573
32	H	-0.5236	2.6953	1.0134	0.0660

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MNDO CHARGES - DEHYDROMUSCARINE (TRANS)(GLOBAL MIN.)

		x	y	z	charge
1	O	2.1154	-0.1193	3.1886	-0.2438
2	C	2.8411	-0.3317	1.9864	0.0884
3	C	2.7649	0.8754	3.8632	-0.0361
4	C	4.3056	-0.0289	2.3309	0.1329
5	C	2.2829	0.5940	0.8962	0.0044
6	H	2.6934	-1.3977	1.6891	0.0817
7	C	4.0283	0.9518	3.4234	-0.1304
8	C	2.1620	1.6983	4.9680	0.1433
9	O	4.9291	-1.1723	2.8685	-0.3049
10	H	4.8969	0.3709	1.4735	0.0547
11	H	2.8117	0.4281	-0.0705	0.0243
12	H	1.1993	0.3966	0.7265	0.0254
13	H	2.3939	1.6699	1.1637	0.0006
14	H	4.7926	1.6442	3.8123	0.0912
15	N	1.9224	0.9234	6.2324	-0.0870
16	H	2.8470	2.5522	5.1803	0.0670
17	H	1.2091	2.1375	4.5912	0.0760
18	H	5.8523	-1.1391	2.6719	0.1934
19	C	3.2012	0.3073	6.7085	0.0804
20	C	1.4117	1.8658	7.2797	0.0814
21	C	0.9030	-0.1515	6.0153	0.0810
22	H	3.0483	-0.2287	7.6735	0.0598
23	H	3.5956	-0.4343	5.9770	0.0758
24	H	3.9832	1.0850	6.8686	0.0557
25	H	1.2188	1.3336	8.2397	0.0628
26	H	2.1490	2.6758	7.4860	0.0590
27	H	0.4578	2.3429	6.9563	0.0621
28	H	1.2636	-0.9263	5.3030	0.0846
29	H	0.6724	-0.6771	6.9705	0.0542
30	H	-0.0486	0.2733	5.6207	0.0622

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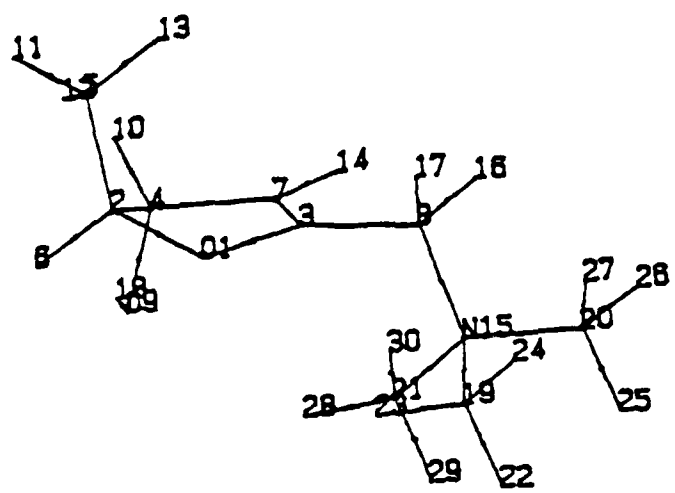

MNDO CHARGES - DEHYDROMUSCARINE (120°) (TRANS)

		x	y	z	charge
1	O	1.4813	-0.0248	-1.4691	-0.2276
2	C	1.4461	-0.5564	-2.7856	0.0628
3	C	0.1916	0.0102	-1.0137	-0.0206
4	C	0.0893	-0.1369	-3.3627	0.1350
5	C	1.6120	-2.0809	-2.7122	0.0063
6	H	2.2978	-0.1094	-3.3524	0.0736
7	C	-0.6397	-0.0889	-2.0597	-0.1230
8	C	-0.1511	0.0016	0.4520	0.1355
9	O	0.1531	1.1605	-3.9074	-0.3066
10	H	-0.3399	-0.8477	-4.1076	0.0528
11	H	1.6134	-2.5267	-3.7334	0.0216
12	H	2.5769	-2.3507	-2.2243	0.0272
13	H	0.7921	-2.5629	-2.1319	-0.0007
14	H	-1.7369	-0.1620	-2.0080	0.0850
15	N	-0.9154	1.2030	0.9358	-0.0864
16	H	-0.7349	-0.9261	0.6559	0.0697
17	H	0.8060	-0.0956	1.0158	0.0822
18	H	0.4566	1.0975	-4.8001	0.1954
19	C	-2.2656	1.3242	0.3039	0.0804
20	C	-1.0979	1.0708	2.4187	0.0814
21	C	-0.1237	2.4422	0.6514	0.0784
22	H	-2.1963	1.5960	-0.7715	0.0697
23	H	-2.8445	0.3779	0.4093	0.0605
24	H	-2.8547	2.1397	0.7832	0.0597
25	H	-1.6897	0.1595	2.6673	0.0609
26	H	-0.1166	0.9974	2.9419	0.0639
27	H	-1.6350	1.9519	2.8397	0.0629
28	H	0.0233	2.5877	-0.4433	0.0767
29	H	-0.6449	3.3460	1.0434	0.0578
30	H	0.8821	2.3931	1.1289	0.0655

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MNDO CHARGES - DEHYDROMUSCARINE (150°) (TRANS)

		x	y	z	charge
1	O	1.5045	-0.0719	-1.4045	-0.2248
2	C	1.5356	-0.6458	-2.7017	0.0625
3	C	0.1954	-0.0549	-0.9992	0.0001
4	C	0.2202	-0.2138	-3.3562	0.1384
5	C	1.6666	-2.1703	-2.5752	0.0060
6	H	2.4250	-0.2305	-3.2335	0.0757
7	C	-0.5762	-0.1238	-2.0934	-0.1427
8	C	-0.1378	0.0297	0.4714	0.1294
9	O	0.3356	1.0688	-3.9260	-0.3039
10	H	-0.1831	-0.9329	-4.1076	0.0493
11	H	1.7167	-2.6454	-3.5819	0.0219
12	H	2.5972	-2.4427	-2.0261	0.0271
13	H	0.8064	-2.6217	-2.0296	-0.0037
14	H	-1.6738	-0.1279	-2.1336	0.0783
15	N	-1.4189	0.7124	0.8666	-0.0831
16	H	-0.0721	-0.9903	0.9161	0.0797
17	H	0.7079	0.6161	0.9003	0.0761
18	H	0.7197	0.9848	-4.7851	0.1943
19	C	-2.6069	-0.1686	0.6357	0.0798
20	C	-1.3503	0.9915	2.3424	0.0804
21	C	-1.5795	2.0199	0.1553	0.0789
22	H	-2.7604	-0.4084	-0.4356	0.0643
23	H	-2.5017	-1.1334	1.1833	0.0618
24	H	-3.5415	0.3245	0.9900	0.0615
25	H	-1.2114	0.0498	2.9225	0.0624
26	H	-0.5038	1.6733	2.5897	0.0661
27	H	-2.2843	1.4794	2.7057	0.0634
28	H	-1.7130	1.8899	-0.9402	0.0734
29	H	-2.4798	2.5631	0.5241	0.0582
30	H	-0.6922	2.6738	0.3195	0.0692

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MNDO CHARGES - DEHYDROMUSCARINE (180°) (TRANS)

		x	y	z	charge
1	O	1.5242	0.0061	-1.3778	-0.2234
2	C	1.5955	-0.5630	-2.6751	0.0613
3	C	0.2091	-0.0238	-0.9923	0.0044
4	C	0.2814	-0.1634	-3.3512	0.1408
5	C	1.7631	-2.0840	-2.5502	0.0066
6	H	2.4835	-0.1230	-3.1891	0.0772
7	C	-0.5400	-0.0951	-2.1025	-0.1477
8	C	-0.1229	0.0765	0.4784	0.1306
9	O	0.3743	1.1215	-3.9193	-0.2999
10	H	-0.0906	-0.8915	-4.1100	0.0461
11	H	1.8445	-2.5546	-3.5569	0.0226
12	H	2.6898	-2.3342	-1.9840	0.0270
13	H	0.9046	-2.5590	-2.0222	-0.0089
14	H	-1.6362	-0.1096	-2.1735	0.0766
15	N	-1.5663	0.0434	0.8981	-0.0826
16	H	0.4203	-0.7652	0.9682	0.0741
17	H	0.3468	1.0204	0.8412	0.0825
18	H	0.7854	1.0518	-4.7668	0.1935
19	C	-2.2235	-1.2432	0.5076	0.0803
20	C	-1.5992	0.1303	2.3994	0.0795
21	C	-2.3191	1.2236	0.3663	0.0787
22	H	-2.2759	-1.3809	-0.5920	0.0656
23	H	-1.6719	-2.1157	0.9274	0.0632
24	H	-3.2704	-1.2847	0.8871	0.0613
25	H	-1.0573	-0.7243	2.8668	0.0637
26	H	-1.1245	1.0716	2.7614	0.0657
27	H	-2.6457	0.1131	2.7827	0.0638
28	H	-2.3787	1.2323	-0.7410	0.0710
29	H	-3.3676	1.2271	0.7435	0.0595
30	H	-1.8390	2.1783	0.6822	0.0669

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T EPIALLOBN.OUT MNDO CHARGES - DEHYDROMUSCARINE (CIS)(GLOBAL MIN.)

		x	y	z	charge
1	O	2.5208	0.0501	5.3531	-0.2407
2	C	3.4877	-0.1416	4.3298	0.0696
3	C	3.0726	0.9422	6.2301	-0.0425
4	C	4.8486	-0.0290	5.0289	0.1311
5	C	3.2249	-1.4681	3.6145	0.0290
6	H	3.3546	0.7035	3.6081	0.0375
7	C	4.4052	0.9230	6.0926	-0.0991
8	C	2.3037	1.7459	7.2412	0.1428
9	O	5.2257	-1.2460	5.6293	-0.3076
10	H	5.6692	0.3563	4.3783	0.0556
11	H	4.0017	-1.6564	2.8383	0.0153
12	H	3.2327	-2.3236	4.3279	0.0192
13	H	2.2305	-1.4597	3.1115	0.0234
14	H	5.1113	1.5139	6.6987	0.0937
15	N	1.8583	0.9407	8.4284	-0.0874
16	H	2.9468	2.5898	7.5844	0.0682
17	H	1.4275	2.2005	6.7232	0.0766
18	H	5.7535	-1.7344	5.0160	0.1963
19	C	3.0453	0.3502	9.1251	0.0791
20	C	1.1349	1.8478	9.3765	0.0819
21	C	0.9326	-0.1580	8.0080	0.0818
22	H	2.7323	-0.2076	10.0377	0.0597
23	H	3.5890	-0.3682	8.4703	0.0764
24	H	3.7609	1.1448	9.4386	0.0567
25	H	0.7880	1.2923	10.2782	0.0626
26	H	1.7956	2.6758	9.7230	0.0593
27	H	0.2404	2.3017	8.8909	0.0621
28	H	0.5468	-0.7118	8.8948	0.0543
29	H	0.0572	0.2484	7.4510	0.0630
30	H	1.4449	-0.9042	7.3604	0.0820

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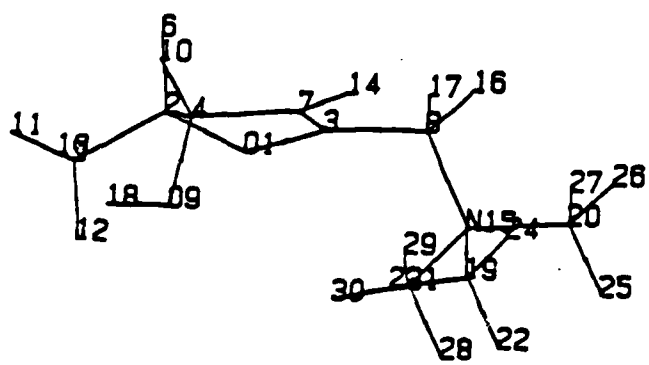

MNDO CHARGE _- EPIALLODEHYDROMUSCARINE(cis)(120°)

		x	y	z	charge
1	O	1.4712	-0.0431	-1.4734	-0.2282
2	C	1.4190	-0.5478	-2.7998	0.0941
3	C	0.1828	0.0023	-1.0135	-0.0108
4	C	0.0688	-0.0937	-3.3652	0.1356
5	C	2.6479	-0.0779	-3.5807	0.0355
6	H	1.4397	-1.6630	-2.7076	0.0346
7	C	-0.6535	-0.0724	-2.0577	-0.1613
8	C	-0.1596	-0.0083	0.4519	0.1348
9	O	0.1406	1.2135	-3.8844	-0.3045
10	H	-0.3476	-0.7953	-4.1267	0.0530
11	H	2.6004	-0.4296	-4.6368	0.0167
12	H	2.7244	1.0334	-3.5887	0.0261
13	H	3.5850	-0.4756	-3.1271	0.0184
14	H	-1.7515	-0.1289	-2.0048	0.0804
15	N	-0.9125	1.2009	0.9366	-0.0869
16	H	-0.7555	-0.9293	0.6511	0.0699
17	H	0.7949	-0.1181	1.0177	0.0832
18	H	-0.4598	1.2925	-4.6087	0.1925
19	C	-2.2546	1.3505	0.2942	0.0820
20	C	-1.1115	1.0591	2.4168	0.0812
21	C	-0.0974	2.4296	0.6720	0.0782
22	H	-2.1712	1.6396	-0.7757	0.0669
23	H	-2.8476	0.4109	0.3801	0.0609
24	H	-2.8369	2.1669	0.7801	0.0594
25	H	-1.6368	1.9460	2.8405	0.0628
26	H	-1.7219	0.1565	2.6515	0.0610
27	H	-0.1367	0.9635	2.9486	0.0644
28	H	0.0679	2.5793	-0.4196	0.0761
29	H	-0.6101	3.3388	1.0624	0.0576
30	H	0.9008	2.3618	1.1630	0.0662

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MNDO CHARGES - EPIALLODEHYDROMUSCARINE (cis)(150°)

		x	y	z	charge
1	O	1.4950	-0.0717	-1.4165	-0.2262
2	C	1.5153	-0.6509	-2.7112	0.0963
3	C	0.1860	-0.0503	-1.0093	0.0081
4	C	0.2084	-0.1966	-3.3679	0.1387
5	C	2.7955	-0.2431	-3.4427	0.0361
6	H	1.5083	-1.7599	-2.5597	0.0309
7	C	-0.5876	-0.1092	-2.1034	-0.1792
8	C	-0.1402	0.0241	0.4638	0.1277
9	O	0.3347	1.0847	-3.9379	-0.3007
10	H	-0.1785	-0.9223	-4.1224	0.0491
11	H	2.8046	-0.6560	-4.4776	0.0158
12	H	2.8915	0.8646	-3.5104	0.0295
13	H	3.6972	-0.6265	-2.9118	0.0177
14	H	-1.6852	-0.1077	-2.1428	0.0732
15	N	-1.4149	0.7112	0.8714	-0.0831
16	H	-0.0803	-1.0006	0.8984	0.0801
17	H	0.7114	0.6002	0.8951	0.0767
18	H	-0.2448	1.1551	-4.6793	0.1910
19	C	-2.6119	-0.1546	0.6300	0.0802
20	C	-1.3407	0.9667	2.3514	0.0803
21	C	-1.5631	2.0305	0.1803	0.0802
22	H	-2.7746	-0.3694	-0.4452	0.0635
23	H	-2.5121	-1.1313	1.1570	0.0626
24	H	-3.5399	0.3395	0.9996	0.0610
25	H	-2.2682	1.4603	2.7236	0.0631
26	H	-1.2126	0.0145	2.9167	0.0629
27	H	-0.4859	1.6345	2.6080	0.0663
28	H	-1.6938	1.9169	-0.9176	0.0701
29	H	-2.4601	2.5753	0.5549	0.0581
30	H	-0.6710	2.6748	0.3562	0.0697

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MNDO CHARGES - EPIALLODEHYDROMUSCARINE (cis)(180°)

		x	y	z	charge
1	O	1.5257	-0.0056	-1.3710	-0.2245
2	C	1.5946	-0.5793	-2.6661	0.0908
3	C	0.2086	-0.0342	-0.9896	0.0115
4	C	0.2898	-0.1626	-3.3497	0.1417
5	C	2.8778	-0.1289	-3.3667	0.0358
6	H	1.6184	-1.6886	-2.5190	0.0269
7	C	-0.5371	-0.1123	-2.1022	-0.1786
8	C	-0.1256	0.0754	0.4803	0.1291
9	O	0.3891	1.1296	-3.9004	-0.2993
10	H	-0.0600	-0.8926	-4.1182	0.0471
11	H	2.9187	-0.5289	-4.4058	0.0138
12	H	2.9454	0.9816	-3.4202	0.0309
13	H	3.7787	-0.4939	-2.8215	0.0179
14	H	-1.6330	-0.1325	-2.1761	0.0718
15	N	-1.5691	0.0443	0.9002	-0.0825
16	H	0.4204	-0.7582	0.9805	0.0751
17	H	0.3407	1.0250	0.8327	0.0820
18	H	-0.0155	1.1430	-4.7526	0.1923
19	C	-2.2146	-1.2562	0.5386	0.0805
20	C	-1.6024	0.1672	2.3991	0.0793
21	C	-2.3320	1.2064	0.3440	0.0798
22	H	-2.2467	-1.4242	-0.5580	0.0652
23	H	-1.6651	-2.1136	0.9911	0.0636
24	H	-3.2666	-1.2922	0.9044	0.0611
25	H	-2.6481	0.1411	2.7842	0.0636
26	H	-1.0457	-0.6662	2.8871	0.0640
27	H	-1.1429	1.1247	2.7376	0.0658
28	H	-2.4139	1.1793	-0.7613	0.0688
29	H	-3.3745	1.2206	0.7377	0.0589
30	H	-1.8489	2.1713	0.6223	0.0674

$

MNDO CHARGES - EPIALLODEHYDROMUSCARINE (cis)(240°)

		x	y	z	charge
1	O	1.5448	-0.0336	-1.3467	-0.2345
2	C	1.5971	-0.5314	-2.6736	0.0904
3	C	0.2249	-0.0243	-0.9741	-0.0128
4	C	0.3179	-0.0150	-3.3372	0.1366
5	C	2.9048	-0.0995	-3.3397	0.0361
6	H	1.5692	-1.6475	-2.5933	0.0168
7	C	-0.5152	-0.0014	-2.0929	-0.1363
8	C	-0.1150	0.0124	0.4982	0.1288
9	O	0.4803	1.3018	-3.8088	-0.2938
10	H	-0.0590	-0.6809	-4.1498	0.0461
11	H	2.9353	-0.4381	-4.4008	0.0135
12	H	3.0234	1.0080	-3.3261	0.0341
13	H	3.7840	-0.5374	-2.8132	0.0156
14	H	-1.6103	0.0333	-2.1731	0.0827
15	N	-0.9201	-1.1139	1.0850	-0.0846
16	H	0.8596	0.0857	1.0348	0.0838
17	H	-0.6507	0.9756	0.6671	0.0731
18	H	0.0831	1.3847	-4.6606	0.1934
19	C	-0.1956	-2.4183	0.9735	0.0838
20	C	-1.1026	-0.8188	2.5488	0.0792
21	C	-2.2857	-1.1933	0.4761	0.0811
22	H	-0.0294	-2.7233	-0.0806	0.0641
23	H	0.8026	-2.3635	1.4658	0.0667
24	H	-0.7739	-3.2362	1.4618	0.0586
25	H	-1.6862	-1.6229	3.0540	0.0624
26	H	-0.1217	-0.7389	3.0720	0.0654
27	H	-1.6479	0.1409	2.7038	0.0636
28	H	-2.2634	-1.4630	-0.5990	0.0626
29	H	-2.9011	-1.9712	0.9842	0.0601
30	H	-2.8212	-0.2204	0.5682	0.0631

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MNDO CHARGES - EPIALLODEHYDROMUSCARINE (cis) (270°)

		x	y	z	charge
1	O	1.5684	-0.5069	-1.3767	-0.2293
2	C	1.4647	-0.9086	-2.7357	0.0837
3	C	0.2867	-0.2822	-0.9510	-0.0458
4	C	0.2736	-0.1271	-3.3043	0.1374
5	C	2.8000	-0.6793	-3.4463	0.0351
6	H	1.2338	-2.0038	-2.7218	0.0164
7	C	-0.4828	-0.0282	-2.0176	-0.1148
8	C	-0.1236	-0.0777	0.4822	0.1381
9	O	0.6611	1.1609	-3.7200	-0.2952
10	H	-0.2667	-0.6609	-4.1220	0.0486
11	H	2.7197	-0.9393	-4.5268	0.0139
12	H	3.1255	0.3832	-3.3692	0.0337
13	H	3.6030	-1.3093	-2.9988	0.0154
14	H	-1.5403	0.2796	-1.9724	0.0893
15	N	-0.4794	-1.3434	1.2002	-0.0888
16	H	0.7156	0.4424	1.0002	0.0828
17	H	-0.9927	0.6207	0.5095	0.0707
18	H	0.3843	1.3065	-4.6104	0.1954
19	C	0.6820	-2.2870	1.2000	0.0843
20	C	-0.8387	-1.0103	2.6162	0.0825
21	C	-1.6525	-1.9947	0.5365	0.0827
22	H	0.9552	-2.5992	0.1665	0.0694
23	H	1.5774	-1.8185	1.6697	0.0681
24	H	0.4406	-3.2129	1.7712	0.0558
25	H	-1.1206	-1.9269	3.1841	0.0618
26	H	0.0180	-0.5320	3.1447	0.0649
27	H	-1.7035	-0.3083	2.6559	0.0610
28	H	-1.4139	-2.2944	-0.5094	0.0622
29	H	-1.9583	-2.9157	1.0844	0.0608
30	H	-2.5295	-1.3076	0.5089	0.0597

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MNDO CHARGES - MUSCARONE (cis)(150°)

		x	y	z	charge
1	O	1.6270	-0.0240	-1.1443	-0.2920
2	C	1.9041	-0.4851	-2.4574	0.0681
3	C	0.2148	-0.0288	-0.9837	0.0996
4	C	0.7975	-1.4621	-2.7864	0.2004
5	C	3.3116	-1.0783	-2.5162	0.0365
6	H	1.8107	0.3911	-3.1430	0.0453
7	C	-0.2728	-1.2794	-1.7319	-0.1021
8	C	-0.1237	0.0310	0.5225	0.0608
9	H	-0.1312	0.8895	-1.5126	0.0187
10	O	0.7698	-2.2748	-3.6767	-0.2010
11	H	3.5576	-1.4259	-3.5460	0.0324
12	H	4.0747	-0.3222	-2.2200	0.0255
13	H	3.4043	-1.9482	-1.8262	0.0139
14	H	-0.2747	-2.1841	-1.0815	0.0579
15	H	-1.2732	-1.1472	-2.2042	0.0554
16	N	-1.4089	0.7014	0.9336	-0.0868
17	H	-0.0963	-1.0087	0.9236	0.0705
18	H	0.7130	0.5653	1.0313	0.0811
19	C	-2.5879	0.0508	0.2808	0.0803
20	C	-1.5555	0.5682	2.4233	0.0829
21	C	-1.3973	2.1626	0.5967	0.0816
22	H	-2.5639	0.1939	-0.8223	0.0590
23	H	-2.6073	-1.0429	0.4935	0.0636
24	H	-3.5432	0.4923	0.6473	0.0638
25	H	-0.7017	1.0481	2.9554	0.0660
26	H	-2.4931	1.0525	2.7819	0.0634
27	H	-1.5930	-0.5029	2.7290	0.0633
28	H	-1.3600	2.3361	-0.5014	0.0630
29	H	-2.3197	2.6642	0.9704	0.0615
30	H	-0.5204	2.6722	1.0581	0.0676

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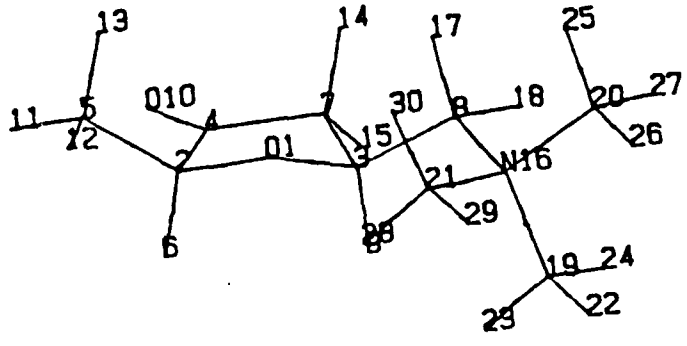

MNDO CHARGES - MUSCARONE (cis)(180°)

		x	y	z	charge
1	O	1.6212	-0.0648	-1.1108	-0.2936
2	C	1.9370	-0.4346	-2.4430	0.0699
3	C	0.2031	-0.0214	-0.9975	0.1009
4	C	0.8298	-1.3719	-2.8631	0.2024
5	C	3.3394	-1.0396	-2.4996	0.0372
6	H	1.8726	0.4872	-3.0696	0.0467
7	C	-0.2748	-1.2115	-1.8413	-0.1084
8	C	-0.1484	-0.0261	0.5068	0.0604
9	H	-0.1106	0.9417	-1.4685	0.0290
10	O	0.8228	-2.1513	-3.7830	-0.2012
11	H	3.6106	-1.3263	-3.5417	0.0323
12	H	4.1012	-0.3118	-2.1365	0.0265
13	H	3.4042	-1.9514	-1.8624	0.0133
14	H	-0.3159	-2.1509	-1.2432	0.0501
15	H	-1.2446	-1.0169	-2.3549	0.0552
16	N	-1.5919	0.0177	0.9399	-0.0861
17	H	0.3309	-0.9267	0.9581	0.0745
18	H	0.3787	0.8538	0.9471	0.0772
19	C	-2.3465	-1.2241	0.5779	0.0806
20	C	-1.6216	0.1461	2.4383	0.0822
21	C	-2.2836	1.2070	0.3481	0.0801
22	H	-2.4823	-1.3187	-0.5199	0.0612
23	H	-1.8261	-2.1339	0.9561	0.0657
24	H	-3.3717	-1.2098	1.0147	0.0621
25	H	-1.1011	1.0722	2.7754	0.0649
26	H	-2.6674	0.1963	2.8203	0.0631
27	H	-1.1238	-0.7248	2.9243	0.0651
28	H	-2.3345	1.1303	-0.7616	0.0596
29	H	-3.3300	1.2892	0.7228	0.0632
30	H	-1.7491	2.1497	0.6076	0.0658

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MNDO CHARGES - MUSCARONE (cis)(210°)

		x	y	z	charge
1	O	1.6434	-0.0273	-1.0909	-0.2957
2	C	1.9673	-0.4340	-2.4104	0.0696
3	C	0.2249	-0.0243	-0.9741	0.0992
4	C	0.8890	-1.4198	-2.7930	0.2033
5	C	3.3879	-0.9964	-2.4506	0.0372
6	H	1.8724	0.4626	-3.0688	0.0493
7	C	-0.2175	-1.2580	-1.7736	-0.1169
8	C	-0.1225	0.0133	0.5308	0.0606
9	H	-0.1201	0.9112	-1.4777	0.0435
10	O	0.9042	-2.2312	-3.6848	-0.2010
11	H	3.6653	-1.3112	-3.4829	0.0326
12	H	4.1273	-0.2327	-2.1162	0.0279
13	H	3.4829	-1.8826	-1.7818	0.0110
14	H	-0.2275	-2.1764	-1.1425	0.0415
15	H	-1.1943	-1.1122	-2.2902	0.0590
16	N	-1.3963	-0.6260	1.0226	-0.0857
17	H	0.7367	-0.4361	1.0823	0.0834
18	H	-0.1372	1.0926	0.8147	0.0699
19	C	-1.3931	-2.1167	0.8789	0.0735
20	C	-1.5361	-0.3118	2.4869	0.0820
21	C	-2.5815	-0.0622	0.3012	0.0795
22	H	-1.4254	-2.4281	-0.1863	0.0673
23	H	-0.4916	-2.5635	1.3575	0.0674
24	H	-2.2933	-2.5658	1.3583	0.0619
25	H	-1.5769	0.7881	2.6626	0.0638
26	H	-2.4707	-0.7492	2.9081	0.0631
27	H	-0.6774	-0.7214	3.0677	0.0657
28	H	-2.5499	-0.3167	-0.7824	0.0591
29	H	-3.5327	-0.4739	0.7106	0.0636
30	H	-2.6163	1.0475	0.3971	0.0644

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MNDO CHARGES - MUSCARONE (trans) (90°)

		x	y	z	charge
1	O	1.6307	-0.0252	-1.1581	-0.3058
2	C	1.8937	0.1957	-2.5371	0.0631
3	C	0.2223	-0.0280	-0.9738	0.0918
4	C	0.5980	0.6613	-3.1676	0.1990
5	C	2.4739	-1.0703	-3.1696	0.0226
6	H	2.6259	1.0360	-2.5835	0.0633
7	C	-0.3605	0.9192	-2.0254	-0.0979
8	C	-0.1187	0.0189	0.5372	0.0733
9	H	-0.0607	-1.0586	-1.3077	0.0417
10	O	0.3400	0.7674	-4.3405	-0.1954
11	H	2.7310	-0.9014	-4.2406	0.0332
12	H	3.4028	-1.3881	-2.6424	0.0281
13	H	1.7460	-1.9123	-3.1188	0.0076
14	H	-1.4121	0.6734	-2.3037	0.0693
15	H	-0.2552	1.9971	-1.7788	0.0383
16	N	-0.6195	1.2707	1.2082	-0.0861
17	H	-0.8952	-0.7642	0.7121	0.0573
18	H	0.7818	-0.3491	1.0838	0.0849
19	C	0.3900	2.3708	1.0911	0.0820
20	C	-0.7948	0.9712	2.6743	0.0801
21	C	-1.9517	1.7146	0.6870	0.0814
22	H	0.5698	2.6580	0.0338	0.0607
23	H	0.0507	3.2849	1.6308	0.0599
24	H	1.3697	2.0593	1.5213	0.0690
25	H	-1.5415	0.1592	2.8341	0.0629
26	H	0.1646	0.6487	3.1411	0.0655
27	H	-1.1494	1.8691	3.2315	0.0633
28	H	-1.9052	2.0421	-0.3709	0.0613
29	H	-2.7023	0.8943	0.7594	0.0632
30	H	-2.3365	2.5848	1.2670	0.0624

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MNDO CHARGES - MUSCARONE (trans)(120^{o})

		x	y	z	charge
1	O	1.6310	-0.0256	-1.1543	-0.3048
2	C	1.9017	0.2004	-2.5307	0.0634
3	C	0.2217	-0.0292	-0.9743	0.0937
4	C	0.6108	0.6712	-3.1658	0.1995
5	C	2.4822	-1.0644	-3.1653	0.0225
6	H	2.6362	1.0391	-2.5699	0.0640
7	C	-0.3575	0.9168	-2.0292	-0.0987
8	C	-0.1188	0.0197	0.5378	0.0725
9	H	-0.0601	-1.0593	-1.3109	0.0405
10	O	0.3616	0.7888	-4.3395	-0.1960
11	H	2.7448	-0.8920	-4.2344	0.0331
12	H	3.4078	-1.3864	-2.6349	0.0283
13	H	1.7522	-1.9050	-3.1213	0.0073
14	H	-1.4030	0.6613	-2.3215	0.0681
15	H	-0.2670	1.9947	-1.7772	0.0390
16	N	-0.7238	1.2337	1.1929	-0.0859
17	H	-0.8256	-0.8236	0.7273	0.0570
18	H	0.8075	-0.2634	1.0917	0.0852
19	C	0.2091	2.4024	1.1057	0.0815
20	C	-0.9180	0.9217	2.6542	0.0801
21	C	-2.0677	1.5849	0.6335	0.0813
22	H	0.4025	2.7032	0.0550	0.0608
23	H	-0.2105	3.2899	1.6331	0.0603
24	H	1.1943	2.1609	1.5671	0.0683
25	H	-1.6148	0.0633	2.7952	0.0631
26	H	0.0477	0.6614	3.1462	0.0656
27	H	-1.3450	1.7939	3.2014	0.0633
28	H	-2.0099	1.9281	-0.4191	0.0612
29	H	-2.7579	0.7111	0.6746	0.0635
30	H	-2.5330	2.4187	1.2079	0.0623

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MNDO CHARGES - F2268 (cis)(150°)

		x	y	z	charge
1	O	1.6221	-0.0270	-1.1486	-0.3052
2	C	1.8433	-0.5907	-2.4278	0.2367
3	C	0.2202	-0.0347	-0.9772	0.0598
4	O	0.7339	-1.3999	-2.7703	-0.2959
5	C	3.1244	-1.4234	-2.4191	0.0171
6	H	1.8877	0.2437	-3.1676	0.0428
7	C	-0.1722	-1.3232	-1.6931	0.1166
8	C	-0.1186	0.0338	0.5236	0.0634
9	H	-0.1485	0.8553	-1.5378	0.0325
10	H	4.0051	-0.7947	-2.1532	0.0248
11	H	3.0542	-2.2511	-1.6763	0.0142
12	H	3.3128	-1.8735	-3.4208	0.0346
13	H	-0.0004	-2.2314	-1.0701	0.0283
14	H	-1.2057	-1.3251	-2.1077	0.0439
15	N	-1.4084	0.7048	0.9175	-0.0873
16	H	-0.0938	-1.0027	0.9332	0.0719
17	H	0.7144	0.5738	1.0326	0.0830
18	C	-2.5744	0.0439	0.2525	0.0783
19	C	-1.5706	0.5835	2.4056	0.0829
20	C	-1.3941	2.1622	0.5660	0.0808
21	H	-2.5321	0.1715	-0.8522	0.0603
22	H	-2.5957	-1.0471	0.4789	0.0636
23	H	-3.5363	0.4879	0.5980	0.0650
24	H	-0.7241	1.0704	2.9428	0.0663
25	H	-2.5137	1.0678	2.7493	0.0639
26	H	-1.6086	-0.4852	2.7198	0.0635
27	H	-1.3449	2.3266	-0.5329	0.0641
28	H	-2.3211	2.6661	0.9248	0.0620
29	H	-0.5233	2.6775	1.0327	0.0679

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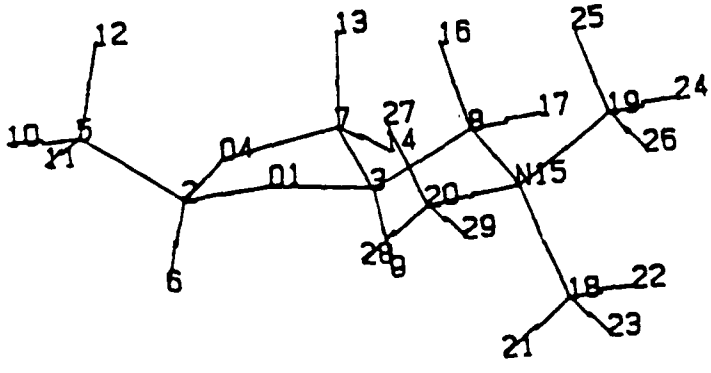

MNDO CHARGES - F2268 (cis)(180°)

		x	y	z	charge
1	O	1.6102	-0.0745	-1.1166	-0.3049
2	C	1.8629	-0.5355	-2.4278	0.2391
3	C	0.2020	-0.0278	-0.9980	0.0621
4	O	0.7983	-1.3842	-2.8036	-0.2946
5	C	3.1891	-1.2922	-2.4756	0.0221
6	H	1.8524	0.3449	-3.1143	0.0370
7	C	-0.2047	-1.2460	-1.8219	0.1137
8	C	-0.1473	-0.0290	0.5023	0.0626
9	H	-0.1218	0.9200	-1.4920	0.0406
10	H	4.0346	-0.6305	-2.1774	0.0252
11	H	3.1727	-2.1651	-1.7833	0.0163
12	H	3.3941	-1.6702	-3.5036	0.0342
13	H	-0.1840	-2.1871	-1.2253	0.0211
14	H	-1.1743	-1.1255	-2.3569	0.0399
15	N	-1.5930	0.0184	0.9253	-0.0869
16	H	0.3310	-0.9265	0.9608	0.0772
17	H	0.3766	0.8537	0.9406	0.0784
18	C	-2.3396	-1.2222	0.5460	0.0787
19	C	-1.6352	0.1405	2.4228	0.0825
20	C	-2.2766	1.2098	0.3292	0.0792
21	H	-2.4539	-1.3133	-0.5547	0.0608
22	H	-1.8249	-2.1331	0.9294	0.0669
23	H	-3.3720	-1.2101	0.9654	0.0634
24	H	-1.1168	1.0649	2.7678	0.0654
25	H	-2.6845	0.1895	2.7953	0.0637
26	H	-1.1425	-0.7328	2.9097	0.0655
27	H	-2.3211	1.1353	-0.7809	0.0605
28	H	-3.3254	1.2937	0.6964	0.0638
29	H	-1.7423	2.1510	0.5946	0.0665

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MNDO CHARGES - F2268 (trans)(120°)

		x	y	z	charge
1	O	1.6065	-0.0121	-1.1843	-0.3173
2	C	1.8061	0.4267	-2.5158	0.2349
3	C	0.2072	-0.0552	-0.9780	0.0570
4	O	0.5441	0.6175	-3.1247	-0.2880
5	C	2.6202	-0.6023	-3.2983	0.0191
6	H	2.3159	1.4183	-2.4647	0.0355
7	C	-0.3458	0.8631	-2.0600	0.1154
8	C	-0.0989	0.0547	0.5349	0.0693
9	H	-0.0617	-1.0940	-1.2954	0.0566
10	H	3.6161	-0.7638	-2.8253	0.0261
11	H	2.0919	-1.5828	-3.3335	0.0180
12	H	2.7881	-0.2626	-4.3462	0.0328
13	H	-1.3683	0.5923	-2.4111	0.0604
14	H	-0.2720	1.9508	-1.8467	0.0079
15	N	-0.9235	1.1684	1.1256	-0.0861
16	H	-0.6071	-0.9002	0.8111	0.0597
17	H	0.8738	0.0112	1.0795	0.0860
18	C	-0.2024	2.4782	1.0305	0.0791
19	C	-1.1183	0.8735	2.5897	0.0806
20	C	-2.2786	1.2658	0.4997	0.0799
21	H	-0.0253	2.7864	-0.0198	0.0623
22	H	-0.7884	3.2925	1.5155	0.0615
23	H	0.7911	2.4250	1.5323	0.0678
24	H	-1.6731	-0.0815	2.7403	0.0638
25	H	-0.1415	0.7886	3.1200	0.0662
26	H	-1.7020	1.6798	3.0912	0.0637
27	H	-2.2254	1.5970	-0.5576	0.0595
28	H	-2.8046	0.2841	0.5333	0.0648
29	H	-2.9100	2.0152	1.0303	0.0635

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MNDO CHARGES - F2268 (trans)(150°)

		x	y	z	charge
1	O	1.6321	-0.0136	-1.1356	-0.3165
2	C	1.8951	0.4341	-2.4530	0.2358
3	C	0.2233	-0.0273	-0.9766	0.0651
4	O	0.6867	0.9202	-3.0014	-0.2895
5	C	2.4422	-0.7072	-3.3092	0.0119
6	H	2.6099	1.2876	-2.3779	0.0521
7	C	-0.1466	1.1388	-1.8875	0.1053
8	C	-0.1003	0.0280	0.5317	0.0622
9	H	-0.1538	-0.9818	-1.4198	0.0537
10	H	3.3904	-1.1051	-2.8801	0.0275
11	H	1.7123	-1.5469	-3.3700	0.0113
12	H	2.6537	-0.3588	-4.3462	0.0341
13	H	-1.2005	1.1363	-2.2475	0.0501
14	H	0.1514	2.1297	-1.4728	0.0167
15	N	-1.3664	0.6648	1.0466	-0.0860
16	H	-0.0332	-1.0201	0.9095	0.0759
17	H	0.7473	0.5677	1.0160	0.0757
18	C	-1.4508	2.1386	0.7980	0.0808
19	C	-1.4076	0.4592	2.5368	0.0816
20	C	-2.5549	-0.0183	0.4445	0.0768
21	H	-1.6361	2.3745	-0.2699	0.0614
22	H	-2.3117	2.5853	1.3467	0.0616
23	H	-0.5241	2.6572	1.1353	0.0690
24	H	-1.3747	-0.6235	2.7994	0.0645
25	H	-0.5450	0.9602	3.0343	0.0664
26	H	-2.3426	0.8752	2.9784	0.0635
27	H	-2.5745	0.1080	-0.6608	0.0598
28	H	-2.5384	-1.1115	0.6597	0.0650
29	H	-3.5052	0.3995	0.8499	0.0642

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MNDO CHARGES - F2268 (trans)(180°)

		x	y	z	charge
1	O	1.6365	-0.0770	-1.1255	-0.3103
2	C	1.9091	0.4770	-2.3985	0.2360
3	C	0.2294	-0.0916	-0.9728	0.0623
4	O	0.7001	0.9402	-2.9639	-0.2900
5	C	2.5434	-0.5739	-3.3090	0.0135
6	H	2.5741	1.3588	-2.2406	0.0499
7	C	-0.2055	1.0435	-1.8912	0.1105
8	C	-0.0884	0.0238	0.5294	0.0597
9	H	-0.1051	-1.0748	-1.3831	0.0435
10	H	3.4966	-0.9529	-2.8738	0.0271
11	H	1.8600	-1.4425	-3.4510	0.0110
12	H	2.7700	-0.1455	-4.3124	0.0341
13	H	-1.2272	0.9225	-2.3170	0.0484
14	H	-0.0672	2.0500	-1.4309	0.0213
15	N	-1.5251	0.0313	0.9844	-0.0866
16	H	0.4290	-0.8380	1.0146	0.0785
17	H	0.4160	0.9404	0.9164	0.0753
18	C	-2.2411	1.2839	0.5839	0.0788
19	C	-1.5380	-0.0416	2.4857	0.0824
20	C	-2.2571	-1.1565	0.4416	0.0795
21	H	-2.3709	1.3529	-0.5160	0.0602
22	H	-3.2658	1.3143	1.0208	0.0635
23	H	-1.6926	2.1887	0.9332	0.0660
24	H	-1.0445	-0.9722	2.8499	0.0655
25	H	-1.0046	0.8288	2.9332	0.0652
26	H	-2.5798	-0.0422	2.8819	0.0635
27	H	-2.3277	-1.1131	-0.6688	0.0609
28	H	-1.7429	-2.1043	0.7227	0.0669
29	H	-3.2983	-1.1986	0.8365	0.0634

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MNDO CHARGES - F2268 (trans)(210°)

		x	y	z	charge
1	O	1.6348	-0.0274	-1.0985	-0.3149
2	C	1.9428	0.5914	-2.3329	0.2361
3	C	0.2249	-0.0243	-0.9741	0.0638
4	O	0.7539	1.1079	-2.8947	-0.2920
5	C	2.5770	-0.4187	-3.2885	0.0136
6	H	2.6198	1.4506	-2.1130	0.0507
7	C	-0.1714	1.1681	-1.8356	0.1171
8	C	-0.1214	0.0131	0.5259	0.0588
9	H	-0.1184	-0.9768	-1.4452	0.0330
10	H	3.5144	-0.8390	-2.8569	0.0257
11	H	1.8816	-1.2652	-3.4921	0.0088
12	H	2.8314	0.0606	-4.2617	0.0348
13	H	-1.1862	1.0900	-2.2871	0.0517
14	H	-0.0249	2.1446	-1.3171	0.0283
15	N	-1.3945	-0.6327	1.0088	-0.0855
16	H	0.7382	-0.4728	1.0464	0.0852
17	H	-0.1130	1.0798	0.8524	0.0680
18	C	-2.6143	0.1080	0.5557	0.0799
19	C	-1.3830	-0.6169	2.5118	0.0824
20	C	-1.4740	-2.0543	0.5461	0.0794
21	H	-2.7529	0.0444	-0.5435	0.0606
22	H	-3.5351	-0.3241	1.0111	0.0633
23	H	-2.5613	1.1829	0.8443	0.0643
24	H	-0.5111	-1.1815	2.9157	0.0660
25	H	-1.3277	0.4262	2.9007	0.0640
26	H	-2.3038	-1.0868	2.9285	0.0635
27	H	-1.5481	-2.1130	-0.5634	0.0625
28	H	-0.5751	-2.6291	0.8676	0.0684
29	H	-2.3747	-2.5604	0.9637	0.0625

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T MEF72N.OUT MNDO CHARGES - 5-METHYLFURMETHIDE (GLOBAL MIN.)

		x	y	z	charge
1	O	3.5875	0.9616	4.0754	-0.0961
2	C	4.5846	0.4381	3.3054	0.0401
3	C	3.8983	0.6294	5.3626	-0.1803
4	C	5.4695	-0.1779	4.0996	-0.1383
5	C	4.6535	0.5533	1.8135	0.0818
6	C	5.0483	-0.0589	5.3613	-0.0260
7	C	3.0847	0.9875	6.5740	0.1643
8	H	6.3857	-0.6954	3.7711	0.1160
9	H	3.7539	0.0835	1.3557	0.0211
10	H	4.6827	1.6261	1.5171	0.0301
11	H	5.5583	0.0514	1.4017	0.0355
12	H	5.5599	-0.4639	6.2498	0.0968
13	N	1.8038	0.2119	6.6928	-0.0914
14	H	2.8776	2.0824	6.5405	0.0717
15	H	3.7106	0.8075	7.4792	0.0682
16	C	2.0891	-1.2579	6.7128	0.0858
17	C	0.8807	0.5267	5.5570	0.0845
18	C	1.1321	0.5955	7.9774	0.0816
19	H	1.1510	-1.8430	6.8522	0.0579
20	H	2.5520	-1.5962	5.7579	0.0655
21	H	2.7829	-1.5185	7.5451	0.0582
22	H	0.6757	1.6206	5.4997	0.0632
23	H	1.3026	0.1982	4.5812	0.0716
24	H	-0.0944	0.0016	5.6810	0.0547
25	H	0.9038	1.6862	7.9983	0.0623
26	H	0.1729	0.0437	8.1097	0.0610
27	H	1.7788	0.3628	8.8547	0.0601

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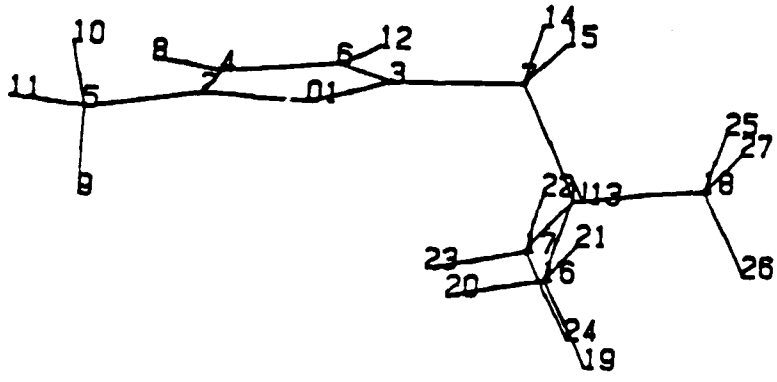


CHARGES FROM MNDO

5-Methylfurmethide (GLOBAL MINIMUM WITH 72.3° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.0961	1.0192
2	C	0.0401	
3	C	-0.1803	
4	C	-0.1383	
5	C	0.0818	
6	C	-0.0260	
7	C	0.1643	
8	H	0.1160	
9	H	0.0211	
10	H	0.0301	
11	H	0.0355	
12	H	0.0968	
13	N	-0.0914	
14	H	0.0717	
15	H	0.0682	
16	C	0.0858	
17	C	0.0845	
18	C	0.0816	
19	H	0.0579	
20	H	0.0655	
21	H	0.0582	
22	H	0.0632	
23	H	0.0716	
24	H	0.0547	
25	H	0.0623	
26	H	0.0610	
27	H	0.0601	

CHARGES FROM MNDO

5-Methylfurmethide (LOCAL MINIMUM WITH 120° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.0796	1.0188
2	C	0.0452	
3	C	-0.1707	
4	C	-0.1404	
5	C	0.0814	
6	C	-0.0446	
7	C	0.1585	
8	H	0.1144	
9	H	0.0338	
10	H	0.0244	
11	H	0.0306	
12	H	0.0867	
13	N	-0.0880	
14	H	0.0676	
15	H	0.0743	
16	C	0.0817	
17	C	0.0834	
18	C	0.0844	
19	H	0.0629	
20	H	0.0612	
21	H	0.0618	
22	H	0.0670	
23	H	0.0570	
24	H	0.0632	
25	H	0.0643	
26	H	0.0620	
27	H	0.0575	

CHARGES FROM MNDO

5-Methylfurmethide (LOCAL MINIMUM WITH 150° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.0803	1.0237
2	C	0.0428	
3	C	-0.1470	
4	C	-0.1386	
5	C	0.0833	
6	C	-0.0635	
7	C	0.1552	
8	H	0.1127	
9	H	0.0328	
10	H	0.0257	
11	H	0.0288	
12	H	0.0796	
13	N	-0.0827	
14	H	0.0754	
15	H	0.0633	
16	C	0.0808	
17	C	0.0840	
18	C	0.0812	
19	H	0.0643	
20	H	0.0622	
21	H	0.0632	
22	H	0.0670	
23	H	0.0576	
24	H	0.0652	
25	H	0.0648	
26	H	0.0631	
27	H	0.0591	

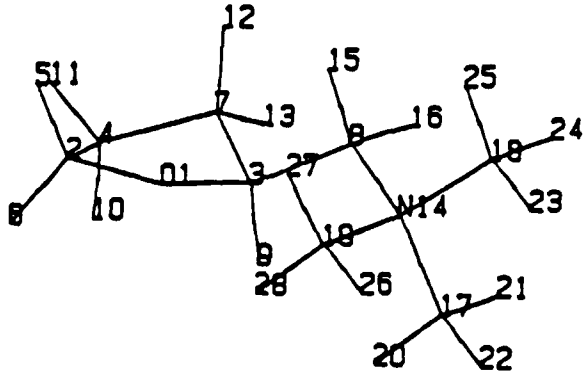
CHARGES FROM MINDO

TFTM (GLOBAL MINIMUM WITH 71.38° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE
1	O	-0.3421
2	C	0.1404
3	C	0.0924
4	C	-0.0513
5	H	0.0285
6	H	0.0419
7	C	-0.0428
8	C	0.0663
9	H	0.0256
10	H	0.0357
11	H	0.0590
12	H	0.0357
13	H	0.0481
14	N	-0.0834
15	H	0.0723
16	H	0.0598
17	C	0.0819
18	C	0.0825
19	C	0.0864
20	H	0.0641
21	H	0.0583
22	H	0.0605
23	H	0.0618
24	H	0.0590
25	H	0.0630
26	H	0.0508
27	H	0.0676
28	H	0.0779

CATIONIC HEAD CHARGE

0.9288



CHARGES FROM MNDO
TFTM (LOCAL MINIMUM WITH 150° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.3128	0.9287
2	C	0.1384	
3	C	0.0990	
4	C	-0.0507	
5	H	0.0334	
6	H	0.0425	
7	C	-0.0556	
8	C	0.0567	
9	H	0.0180	
10	H	0.0330	
11	H	0.0572	
12	H	0.0372	
13	H	0.0316	
14	N	-0.0857	
15	H	0.0673	
16	H	0.0805	
17	C	0.0811	
18	C	0.0834	
19	C	0.0819	
20	H	0.0628	
21	H	0.0611	
22	H	0.0599	
23	H	0.0616	
24	H	0.0623	
25	H	0.0655	
26	H	0.0640	
27	H	0.0591	
28	H	0.0672	

CHARGES FROM MNDO

TFTM (LOCAL MINIMUM WITH 180° DIHEDRAL ANGLE)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	O	-0.3130	0.9240
2	C	0.1400	
3	C	0.1003	
4	C	-0.0498	
5	H	0.0252	
6	H	0.0495	
7	C	-0.0594	
8	C	0.0538	
9	H	0.0285	
10	H	0.0375	
11	H	0.0568	
12	H	0.0288	
13	H	0.0315	
14	N	-0.0845	
15	H	0.0721	
16	H	0.0754	
17	C	0.0809	
18	C	0.0827	
19	C	0.0813	
20	H	0.0646	
21	H	0.0597	
22	H	0.0613	
23	H	0.0612	
24	H	0.0643	
25	H	0.0646	
26	H	0.0601	
27	H	0.0607	
28	H	0.0658	

CHARGES FROM MNDO

ARECOLINE (H,CH_3) S-TRANS

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	C	0.0464	0.9365
2	C	-0.0393	
3	C	-0.2288	
4	H	0.1220	
5	C	0.0446	
6	H	0.0605	
7	H	0.0839	
8	C	0.1199	
9	C	0.3985	
10	N	-0.0486	
11	H	0.0794	
12	H	0.0757	
13	H	0.0889	
14	H	0.0823	
15	O	-0.3237	
16	O	-0.3061	
17	C	0.0792	
18	H	0.2109	
19	C	0.2029	
20	H	0.0694	
21	H	0.0719	
22	H	0.0629	
23	H	0.0440	
24	H	-0.0185	
25	H	0.0219	

CHARGE FROM MNDO

ARECOLINE (H,CH_3) S-CIS

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	C	0.0496	0.9235
2	C	-0.0398	
3	C	-0.2230	
4	H	0.1289	
5	C	0.0434	
6	H	0.0587	
7	H	0.0879	
8	C	0.1165	
9	C	0.3897	
10	N	-0.0477	
11	H	0.0825	
12	H	0.0758	
13	H	0.0738	
14	H	0.0872	
15	O	-0.3452	
16	O	-0.2777	
17	C	0.0796	
18	H	0.2089	
19	C	0.2041	
20	H	0.0664	
21	H	0.0733	
22	H	0.0638	
23	H	0.0386	
24	H	-0.0234	
25	H	0.0281	

CHARGES FROM MINDO

TROPINE DERIVATIVE (R = $-OCOCH_3$)

SEQ. NO.	TYPE	CHARGE	CATIONIC HEAD CHARGE
1	N	-0.0392	0.6568
2	C	0.0179	
3	C	0.0173	
4	C	0.0839	
5	H	0.2113	
6	C	-0.0602	
7	C	-0.0333	
8	H	0.0862	
9	C	-0.0581	
10	C	-0.0332	
11	H	0.0867	
12	H	0.0719	
13	H	0.0600	
14	H	0.0608	
15	C	0.1293	
16	H	0.0492	
17	H	0.0733	
18	H	0.0455	
19	H	0.0820	
20	H	0.0481	
21	H	0.0870	
22	H	0.0861	
23	H	0.0439	
24	O	-0.2749	
25	H	0.0347	
26	C	0.3371	
27	C	0.0307	
28	O	-0.3672	
29	H	0.0424	
30	H	0.0332	
31	H	0.0476	

CHART XI

MNDO Charges for Pilocarpine

1	C	5.5236	1.5396	3.9764	0.2004
2	N	6.2940	2.6541	3.7812	-0.1700
3	N	5.9490	0.9317	5.1355	-0.1995
4	H	4.7191	1.2035	3.3207	0.1886
5	C	7.2258	2.7715	4.8213	0.0303
6	H	6.2043	3.2913	3.0093	0.2723
7	C	7.0163	1.6959	5.6885	0.0027
8	C	5.3669	-0.3320	5.6656	0.1927
9	H	7.9413	3.5876	4.8509	0.1620
10	C	7.7863	1.3276	6.9318	0.0628
11	H	4.9494	-0.1520	6.6794	0.0520
12	H	6.1568	-1.1130	5.7061	0.0517
13	H	4.5509	-0.6769	4.9949	0.0434
14	C	7.7628	2.3943	8.0546	-0.0912
15	H	8.8438	1.1646	6.6108	0.0477
16	H	7.4447	0.3501	7.3379	0.0359
17	C	8.6815	2.0847	9.2822	-0.0413
18	C	6.3513	2.6719	8.6840	0.1647
19	H	8.1025	3.3514	7.5901	0.0342
20	C	7.8281	2.6081	10.4605	0.3206
21	C	10.1378	2.6032	9.2274	-0.0060
22	H	8.7574	0.9771	9.4186	0.0497
23	O	6.5608	2.9508	10.0440	-0.2762
24	H	5.8483	3.5465	8.2064	0.0283
25	H	5.6601	1.7971	8.5855	0.0054
26	O	8.0923	2.7213	11.6428	-0.2479
27	C	10.3914	4.1129	9.2010	0.0218
28	H	10.6302	2.1527	8.3334	0.0058
29	H	10.6732	2.1820	10.1106	0.0392
30	H	11.4823	4.3048	9.2644	0.0183
31	H	10.0295	4.5789	8.2617	-0.0157
32	H	9.9121	4.6406	10.0482	0.0173

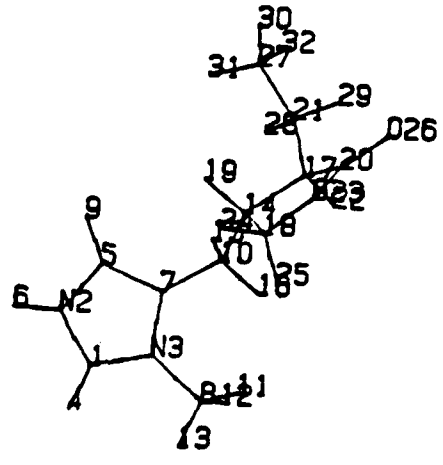


TABLE V

MNDO CHARGES- ATROPINE- 90°

Cationic Head Charge 0.6573

1	C	0.1404	-1.6182	-2.9715	0.0121
2	C	0.0425	-0.4056	-3.9165	-0.0365
3	C	-0.4339	-1.3079	-1.5762	-0.0450
4	N	1.6031	-1.8429	-2.8136	-0.0401
5	H	-0.3641	-2.5267	-3.3816	0.0902
6	C	1.3496	0.3761	-3.6675	-0.0366
7	H	-0.8692	0.2052	-3.7189	0.0711
8	H	-0.0153	-0.7419	-4.9790	0.0508
9	C	0.1789	-0.0356	-0.9706	0.1448
10	H	-1.5439	-1.2039	-1.6299	0.0750
11	H	-0.2207	-2.1755	-0.9071	0.0480
12	C	2.0939	-0.4535	-2.6034	0.0127
13	C	2.2201	-2.5001	-3.9968	0.0831
14	H	1.7909	-2.4128	-1.9768	0.2158
15	H	1.9515	0.4395	-4.6051	0.0510
16	H	1.1671	1.4221	-3.3270	0.0723
17	C	1.7022	-0.0417	-1.1725	-0.0661
18	O	-0.1268	-0.0150	0.4131	-0.3210
19	H	-0.2859	0.8538	-1.4615	0.0300
20	H	3.2045	-0.3984	-2.7110	0.0915
21	H	2.0615	-1.9338	-4.9412	0.0695
22	H	3.3146	-2.6132	-3.8268	0.0618
23	H	1.7925	-3.5212	-4.1158	0.0607
24	H	2.1224	0.9674	-0.9503	0.0857
25	H	2.1685	-0.7574	-0.4542	0.0513
26	C	-0.2417	1.2219	0.9357	0.3337
27	O	0.7793	1.8201	1.1849	-0.2796
28	C	-1.6286	1.8364	1.0709	0.0220
29	C	-2.5576	0.9383	1.9008	0.1716
30	C	-1.5928	3.2685	1.5767	-0.0860
31	H	-2.0315	1.8341	0.0302	0.0340
32	O	-3.8555	1.4865	1.8742	-0.3238
33	H	-2.2373	0.8619	2.9653	0.0043
34	H	-2.6354	-0.0881	1.4716	-0.0103
35	C	-1.2348	3.5487	2.8432	-0.0243
36	C	-1.9171	4.2961	0.7696	-0.0275
37	H	-4.3921	1.0689	2.5291	0.1902
38	C	-1.2042	4.8126	3.2938	-0.0531
39	H	-0.9557	2.7339	3.5317	0.0534
40	C	-1.8885	5.5633	1.2113	-0.0574
41	H	-2.2138	4.1082	-0.2762	0.0476
42	C	-1.5320	5.8250	2.4775	-0.0307
43	H	-0.9075	5.0205	4.3366	0.0686
44	H	-2.1585	6.3916	0.5333	0.0662
45	H	-1.5072	6.8658	2.8445	0.0689

ATROPINE 90°

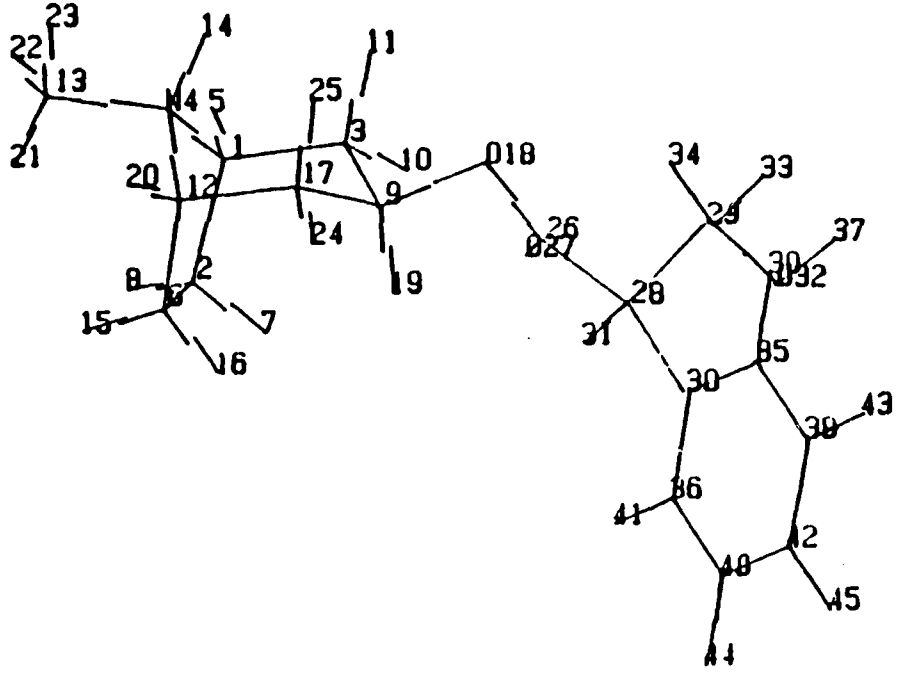

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TABLE V

MNDO CHARGES - ATROPINE 120°

Cationic Head Charge 0.6565

1	C	0.2073	-1.6276	-2.9607	0.0133
2	C	0.1197	-0.4233	-3.9175	-0.0365
3	C	-0.3921	-1.3077	-1.5776	-0.0561
4	N	1.6690	-1.8445	-2.7794	-0.0402
5	H	-0.2871	-2.5414	-3.3710	0.0899
6	C	1.4210	0.3647	-3.6575	-0.0368
7	H	-0.7964	0.1865	-3.7379	0.0709
8	H	0.0772	-0.7688	-4.9778	0.0509
9	C	0.2136	-0.0321	-0.9744	0.1450
10	H	-1.5007	-1.2035	-1.6521	0.0729
11	H	-0.1911	-2.1690	-0.8971	0.0481
12	C	2.1520	-0.4511	-2.5740	0.0118
13	C	2.3046	-2.5093	-3.9486	0.0831
14	H	1.8464	-2.4081	-1.9362	0.2153
15	H	2.0364	0.4196	-4.5869	0.0509
16	H	1.2315	1.4140	-3.3316	0.0741
17	C	1.7388	-0.0295	-1.1511	-0.0536
18	O	-0.0899	0.0103	0.4097	-0.3233
19	H	-0.2232	0.8601	-1.4862	0.0341
20	H	3.2638	-0.3927	-2.6654	0.0911
21	H	2.1565	-1.9522	-4.9002	0.0698
22	H	3.3972	-2.6161	-3.7629	0.0617
23	H	1.8832	-3.5333	-4.0643	0.0607
24	H	2.1434	0.9840	-0.9177	0.0841
25	H	2.1974	-0.7402	-0.4230	0.0482
26	C	-0.8130	1.0807	0.7925	0.3305
27	O	-0.2205	2.1243	0.9407	-0.2699
28	C	-2.3265	0.9514	0.8915	0.0229
29	C	-2.7254	-0.1789	1.8515	0.1711
30	C	-3.0120	2.2673	1.2185	-0.0868
31	H	-2.6374	0.6294	-0.1308	0.0294
32	O	-4.1225	-0.3520	1.7889	-0.3246
33	H	-2.4513	0.0438	2.9083	0.0063
34	H	-2.2705	-1.1537	1.5571	-0.0121
35	C	-2.8712	2.8413	2.4275	-0.0242
36	C	-3.7765	2.8959	0.3059	-0.0273
37	H	-4.4144	-0.8638	2.5268	0.1905
38	C	-3.4755	4.0034	2.7204	-0.0526
39	H	-2.2472	2.3595	3.1985	0.0537
40	C	-4.3838	4.0590	0.5896	-0.0572
41	H	-3.9150	2.4590	-0.6975	0.0467
42	C	-4.2352	4.6161	1.8005	-0.0302
43	H	-3.3463	4.4574	3.7183	0.0691
44	H	-5.0066	4.5582	-0.1731	0.0663
45	H	-4.7330	5.5724	2.0376	0.0693

ATROPINE 120°

TABLE V

MNDO CHARGES - ATROPINE 150°

Cationic Head Charge 0.6571

1	C	0.2959	-1.5613	-3.0468	0.0151
2	C	0.3275	-0.3020	-3.9338	-0.0365
3	C	-0.3960	-1.2923	-1.6965	-0.0660
4	N	1.7299	-1.8524	-2.7729	-0.0402
5	H	-0.2020	-2.4277	-3.5463	0.0899
6	C	1.6357	0.4124	-3.5338	-0.0365
7	H	-0.5741	0.3369	-3.7843	0.0730
8	H	0.3504	-0.5845	-5.0132	0.0509
9	C	0.2224	-0.0903	-0.9688	0.1390
10	H	-1.4855	-1.1214	-1.8634	0.0703
11	H	-0.2970	-2.2008	-1.0561	0.0474
12	C	2.2518	-0.4954	-2.4520	0.0109
13	C	2.4238	-2.4773	-3.9310	0.0830
14	H	1.8205	-2.4708	-1.9550	0.2149
15	H	2.3199	0.4931	-4.4117	0.0506
16	H	1.4647	1.4489	-3.1603	0.0758
17	C	1.7554	-0.1393	-1.0381	-0.0418
18	O	-0.1679	-0.0818	0.3943	-0.3185
19	H	-0.1116	0.8611	-1.4487	0.0425
20	H	3.3688	-0.4811	-2.4617	0.0908
21	H	2.3689	-1.8615	-4.8559	0.0702
22	H	3.4945	-2.6424	-3.6741	0.0616
23	H	1.9719	-3.4737	-4.1374	0.0609
24	H	2.1830	0.8395	-0.7143	0.0826
25	H	2.1318	-0.9117	-0.3258	0.0448
26	C	-1.3211	0.5629	0.6624	0.3289
27	O	-1.3408	1.7658	0.5393	-0.2769
28	C	-2.5565	-0.2491	1.0275	0.0263
29	C	-2.2932	-1.1413	2.2492	0.1709
30	C	-3.7940	0.6184	1.1841	-0.0868
31	H	-2.7076	-0.9337	0.1603	0.0296
32	O	-3.4157	-1.9683	2.4541	-0.3248
33	H	-2.1226	-0.5522	3.1794	0.0058
34	H	-1.4233	-1.8202	2.0873	-0.0105
35	C	-3.9216	1.4639	2.2233	-0.0228
36	C	-4.7924	0.5704	0.2822	-0.0285
37	H	-3.3811	-2.3445	3.3195	0.1903
38	C	-5.0109	2.2354	2.3627	-0.0524
39	H	-3.1212	1.5379	2.9781	0.0541
40	C	-5.8851	1.3389	0.4130	-0.0574
41	H	-4.7237	-0.1069	-0.5859	0.0453
42	C	-5.9974	2.1744	1.4562	-0.0302
43	H	-5.0950	2.9230	3.2223	0.0692
44	H	-6.6924	1.2848	-0.3380	0.0659
45	H	-6.8943	2.8084	1.5669	0.0692

ATROPINE 150

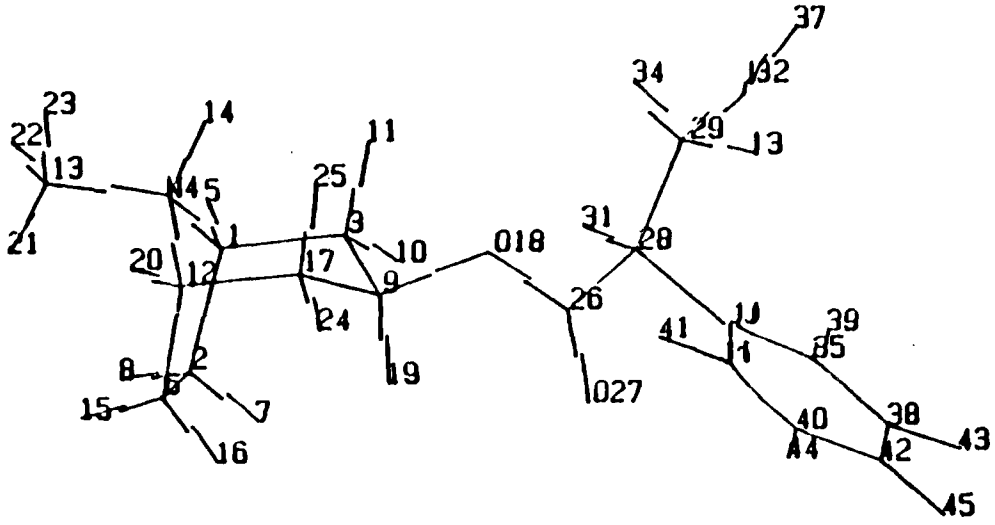


TABLE V

MNDO CHARGES - ATROPINE 240°

Cationic Head Charge 0.6624

1	C	-0.0826	-2.0841	-2.3037	0.0247
2	C	0.5946	-1.9254	-3.6812	-0.0399
3	C	-0.8445	-0.8067	-1.8864	-0.0591
4	N	1.0634	-2.2941	-1.3806	-0.0774
5	H	-0.7849	-2.9527	-2.2887	0.0897
6	C	1.9936	-1.3691	-3.3603	-0.0400
7	H	0.0271	-1.2615	-4.3739	0.0639
8	H	0.6774	-2.9153	-4.1904	0.0481
9	C	-0.0120	0.1689	-1.0355	0.1349
10	H	-1.1878	-0.2747	-2.8038	0.0645
11	H	-1.7957	-1.0663	-1.3659	0.0480
12	C	2.0061	-1.2342	-1.8233	0.0190
13	C	1.6278	-3.6669	-1.4541	0.0941
14	H	0.7474	-2.1562	-0.4059	0.2537
15	H	2.7834	-2.0833	-3.6950	0.0469
16	H	2.1957	-0.4073	-3.8865	0.0657
17	C	1.4880	0.1513	-1.3764	-0.0449
18	O	-0.1386	0.0332	0.3706	-0.3353
19	H	-0.4025	1.2025	-1.2023	0.0686
20	H	3.0292	-1.4008	-1.4068	0.0870
21	H	1.9745	-3.9437	-2.4741	0.0534
22	H	2.4864	-3.7485	-0.7501	0.0562
23	H	0.8568	-4.4006	-1.1271	0.0620
24	H	1.7040	0.9123	-2.1619	0.0609
25	H	2.0633	0.4899	-0.4819	0.0658
26	C	-0.7968	-0.9884	0.9372	0.4063
27	O	-0.3842	-2.0974	0.6702	-0.3861
28	C	-1.9047	-0.7165	1.9424	0.0274
29	C	-2.9546	0.2495	1.3746	0.1713
30	C	-2.5246	-2.0011	2.4636	-0.0923
31	H	-1.3884	-0.1875	2.7786	0.0745
32	O	-3.9046	0.5190	2.3788	-0.3135
33	H	-3.4984	-0.1773	0.5007	-0.0135
34	H	-2.5030	1.2262	1.0810	-0.0024
35	C	-3.2149	-2.8150	1.6438	-0.0371
36	C	-2.3962	-2.3607	3.7543	-0.0147
37	H	-4.5782	1.0905	2.0461	0.1945
38	C	-3.7627	-3.9535	2.0964	-0.0565
39	H	-3.3347	-2.5537	0.5789	0.0353
40	C	-2.9404	-3.4979	4.2150	-0.0517
41	H	-1.8360	-1.7196	4.4557	0.0627
42	C	-3.6264	-4.2980	3.3855	-0.0273
43	H	-4.3244	-4.6083	1.4077	0.0662
44	H	-2.8238	-3.7762	5.2770	0.0740
45	H	-4.0749	-5.2342	3.7608	0.0725

ATROPINE 240°

TABLE VI

MNDO CHARGES - DIBENAMINE 110°

Cationic Head Charge o.6418

1	C	1.1726	1.1852	0.1244	0.0100
2	C	0.7621	-0.2931	-0.0113	-0.0340
3	C	1.0102	1.6953	1.5672	-0.0526
4	N	0.1877	1.9204	-0.7131	-0.0389
5	H	2.2168	1.3790	-0.2223	0.0866
6	C	-0.7541	-0.2376	-0.2945	-0.0342
7	H	1.0103	-0.8810	0.9032	0.0712
8	H	1.3018	-0.7722	-0.8625	0.0471
9	C	-0.3801	1.3706	2.1525	0.1324
10	H	1.8257	1.2713	2.1960	0.0711
11	H	1.1627	2.8011	1.5680	0.0431
12	C	-1.0838	1.2675	-0.3015	0.0113
13	C	0.4592	1.8019	-2.1699	0.0837
14	H	0.1743	2.9157	-0.4493	0.2158
15	H	-0.9829	-0.6923	-1.2876	0.0471
16	H	-1.3562	-0.7918	0.4629	0.0707
17	C	-1.4289	1.7907	1.1053	-0.0578
18	O	-0.5457	2.1636	3.3109	-0.3050
19	H	-0.4401	0.2903	2.4089	0.0367
20	H	-1.9120	1.5265	-1.0051	0.0859
21	H	0.4866	0.7472	-2.5230	0.0682
22	H	-0.3278	2.3484	-2.7370	0.0595
23	H	1.4357	2.2831	-2.4034	0.0597
24	H	-2.4520	1.4543	1.3844	0.0721
25	H	-1.4781	2.9050	1.0633	0.0422
26	C	-1.0294	1.6168	4.5319	0.2124
27	C	-2.4460	1.0737	4.6390	-0.0817
28	C	-0.0880	0.8594	5.4462	-0.0809
29	H	-1.0350	2.6080	5.0263	0.0355
30	C	-3.1812	1.3936	5.7276	-0.0573
31	C	-2.9950	0.2339	3.7428	-0.0555
32	C	-0.2935	0.8347	6.7860	-0.0481
33	C	0.9700	0.1924	4.9494	-0.0528
34	C	-2.5834	2.2488	6.8259	0.0300
35	C	-4.4329	0.9190	5.8656	-0.0321
36	C	-4.2434	-0.2379	3.8777	-0.0549
37	H	-2.4318	-0.1150	2.8693	0.0250
38	C	-1.4441	1.5001	7.5404	0.0303
39	C	0.5781	0.1510	7.5561	-0.0408
40	C	1.8279	-0.4837	5.7255	-0.0531
41	H	1.1700	0.1745	3.8729	0.0243
42	H	-3.3599	2.5023	7.5866	0.0188
43	H	-2.2754	3.2524	6.4534	0.0199
44	C	-4.9748	0.1131	4.9427	-0.0367
45	H	-5.0334	1.1772	6.7543	0.0709
46	H	-4.6658	-0.9219	3.1207	0.0619
47	H	-1.9323	0.6867	8.1295	0.0145
48	H	-0.9946	2.2049	8.2802	0.0199
49	C	1.6312	-0.5031	7.0484	-0.0370
50	H	0.4313	0.1162	8.6496	0.0670
51	H	2.6859	-1.0196	5.2828	0.0626
52	H	-6.0009	-0.2742	5.0682	0.0733
53	H	2.3240	-1.0538	7.7083	0.0727

DIBENAMINE 110°

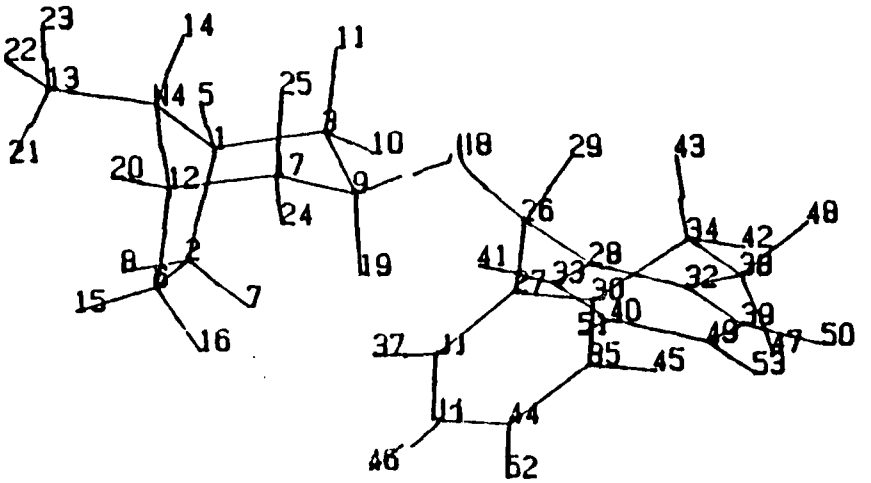


TABLE VII

MNDO CHARGES - QUINUCLIDINE 0^{o}

Cationic Head Charge 0.7373

1	N	1.1989	-1.7600	-2.8914	-0.0386
2	C	1.2855	-0.4022	-3.8257	0.0434
3	C	0.1196	-1.5192	-1.8914	0.0316
4	C	2.5030	-1.9301	-2.1900	0.0444
5	H	0.9892	-2.6144	-3.4278	0.2150
6	C	1.6729	0.6737	-3.0591	-0.0355
7	H	0.3025	-0.4808	-4.3385	0.0696
8	H	2.0309	-0.8320	-4.6230	0.0711
9	C	0.3358	-0.1853	-1.1495	0.1651
10	H	0.1019	-2.3761	-1.1778	0.0834
11	H	-0.8668	-1.5271	-2.4118	0.0762
12	C	2.8193	-0.6875	-1.3429	-0.0306
13	H	3.3004	-2.1169	-2.9471	0.0700
14	H	2.4553	-2.8448	-1.5532	0.0712
15	C	1.7191	0.3682	-1.5463	-0.0987
16	H	2.6678	1.0472	-3.4010	0.0604
17	H	0.9422	1.4909	-3.2694	0.0620
18	O	0.0527	-0.3799	0.2224	-0.3293
19	H	-0.4368	0.5520	-1.4744	0.0606
20	H	2.9036	-0.9622	-0.2686	0.0589
21	H	3.8112	-0.2643	-1.6299	0.0643
22	H	1.9580	1.3200	-1.0147	0.1153
23	C	0.8649	-0.1335	1.2664	0.3655
24	O	1.6650	0.7695	1.2512	-0.3247
25	C	0.6131	-1.0130	2.4891	0.0843
26	C	1.3191	-0.6477	3.7832	-0.0939
27	C	0.8232	-2.4795	2.1577	-0.0884
28	H	-0.4750	-0.8343	2.6560	0.0436
29	C	0.6343	-0.6408	4.9433	-0.0297
30	C	2.6294	-0.3433	3.8290	-0.0250
31	C	-0.1785	-3.3695	2.2839	-0.0295
32	C	2.0159	-2.9290	1.7273	-0.0648
33	C	1.2277	-0.3312	6.1065	-0.0555
34	H	-0.4394	-0.8948	4.9542	0.0560
35	C	3.2327	-0.0323	4.9872	-0.0573
36	H	3.2370	-0.3450	2.9098	0.0505
37	C	0.0028	-4.6656	1.9859	-0.0547
38	H	-1.1711	-3.0409	2.6357	0.0685
39	C	2.2069	-4.2224	1.4259	-0.0704
40	H	2.8618	-2.2336	1.6135	0.0516
41	C	2.5326	-0.0237	6.1311	-0.0294
42	H	0.6440	-0.3311	7.0435	0.0707
43	H	4.3085	0.2155	5.0003	0.0671
44	C	1.1977	-5.0958	1.5545	-0.0440
45	H	-0.8321	-5.3796	2.0948	0.0744
46	H	3.1938	-4.5679	1.0718	0.0635
47	H	3.0268	0.2309	7.0848	0.0706
48	H	1.3495	-6.1609	1.3078	0.0715

QUINUCLIDINE 0^{o}

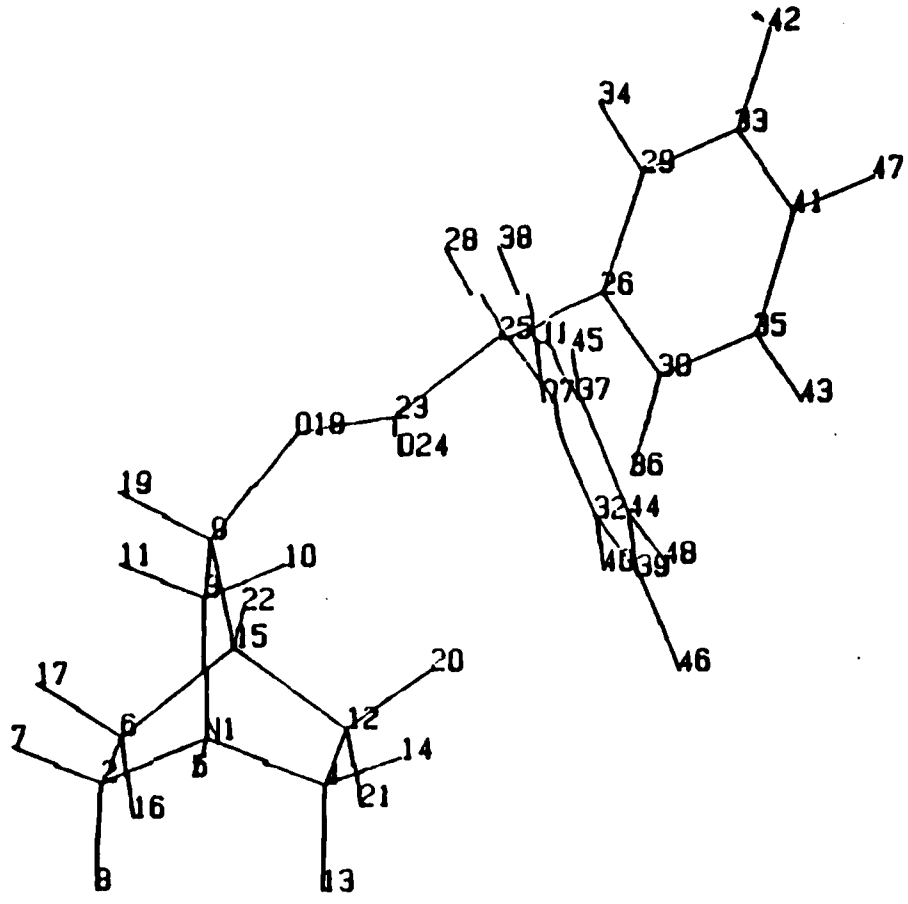
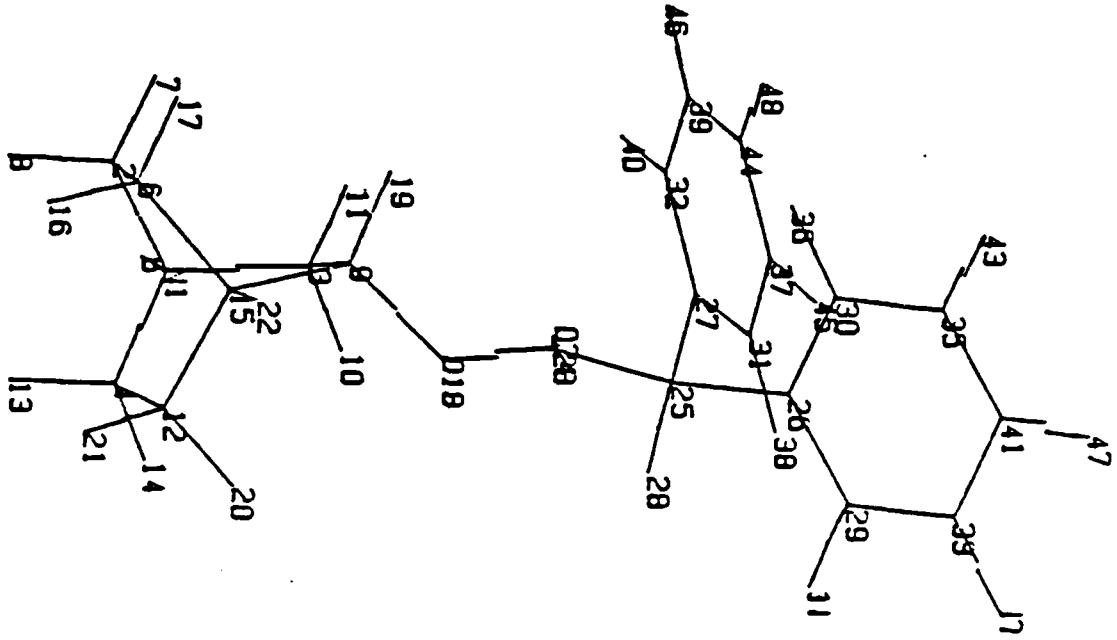


TABLE VII

MNDO CHARGES - QUINUCLIDINE 180°

Cationic Head Charge 0.7479

1	N	0.8068	-2.1027	-2.3882	-0.0413
2	C	1.3826	-1.1455	-3.3733	0.0443
3	C	-0.3010	-1.4503	-1.6299	0.0282
4	C	1.8648	-2.5386	-1.4338	0.0458
5	H	0.4334	-2.9253	-2.8841	0.2160
6	C	2.0581	0.0240	-2.6369	-0.0359
7	H	0.5667	-0.7854	-4.0432	0.0696
8	H	2.1131	-1.6820	-4.0232	0.0708
9	C	0.1604	-0.1036	-1.0230	0.1455
10	H	-0.6272	-2.1808	-0.8549	0.0919
11	H	-1.1617	-1.2920	-2.3212	0.0821
12	C	2.3093	-1.3466	-0.5696	-0.0302
13	H	2.7191	-2.9656	-2.0099	0.0676
14	H	1.4703	-3.3655	-0.7978	0.0729
15	C	1.6967	-0.0565	-1.1427	-0.0747
16	H	3.1668	-0.0213	-2.7564	0.0575
17	H	1.7272	0.9993	-3.0672	0.0619
18	O	-0.1806	0.0359	0.3450	-0.3038
19	H	-0.2825	0.7673	-1.5645	0.0537
20	H	1.9799	-1.4804	0.4881	0.0665
21	H	3.4229	-1.2735	-0.5529	0.0611
22	H	2.0969	0.8371	-0.6026	0.0948
23	C	-1.4851	0.0254	0.6854	0.3587
24	O	-2.2359	-0.7408	0.1252	-0.3495
25	C	-1.9215	0.9679	1.8026	0.0907
26	C	-3.3396	0.7099	2.2757	-0.1003
27	C	-1.7350	2.4369	1.4662	-0.0872
28	H	-1.2108	0.7158	2.6245	0.0420
29	C	-3.5850	0.2541	3.5182	-0.0304
30	C	-4.3886	0.9241	1.4605	-0.0207
31	C	-1.4362	3.3236	2.4339	-0.0265
32	C	-1.8790	2.8983	0.2100	-0.0575
33	C	-4.8386	0.0163	3.9345	-0.0575
34	H	-2.7511	0.0659	4.2155	0.0549
35	C	-5.6450	0.6889	1.8685	-0.0570
36	H	-4.2266	1.2953	0.4350	0.0518
37	C	-1.2772	4.6275	2.1581	-0.0479
38	H	-1.3203	2.9800	3.4760	0.0644
39	C	-1.7220	4.2003	-0.0753	-0.0560
40	H	-2.1340	2.2086	-0.6114	0.0356
41	C	-5.8732	0.2329	3.1089	-0.0301
42	H	-5.0198	-0.3591	4.9567	0.0690
43	H	-6.4918	0.8693	1.1836	0.0673
44	C	-1.4192	5.0698	0.8999	-0.0360
45	H	-1.0316	5.3375	2.9669	0.0732
46	H	-1.8442	4.5574	-1.1127	0.0636
47	H	-6.9053	0.0373	3.4480	0.0694
48	H	-1.2905	6.1416	0.6692	0.0716



Appendix B. Reprints and Preprints of Articles Acknowledging Army Support